AUTO1-1070
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

CLINICOPATHOLOGICAL STUDIES IN LAMBS REPETITIVELY INOCULATED WITH PRODUCTS CONTAINING ALUMINIUM ADJUVANTS

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The use of aluminum-containing vaccine adjuvants is widespread in the Spanish small ruminant industry. These compounds were related to an episode of vaccine adverse reactions which gave rise to a process known today as the ovine ASIA syndrome. An in vivo model of this syndrome was established. Eighty-four lambs were selected, divided into three groups (n=28 each) and submitted to an intensive inoculation program with: i) Vaccines containing aluminum hydroxide as adjuvant; ii) The adjuvant only; iii) PBS. Nineteen inoculations were performed during 15 months. A comprehensive in vivo follow-up was performed, including clinical examinations and behavioral and cognitive tests. After euthanasia, the pathology of different tissues was studied grossly, microscopically and by electron microscopy. The presence of aluminum in tissues was studied by energy dispersive X-ray spectroscopy, graphite furnace atomic absorption spectroscopy and lumogallion fluorescent staining. Animals in the vaccinated and adjuvant-inoculated groups presented persistent injection-site granulomas with intramacrophagic aluminum. Persistency was higher in the vaccinated group ($p<0.001$), reaching 15 months in some cases. There was translocation of aluminum to the regional lymph nodes ($p<0.001$) and lumbar spinal cord ($p<0.001$). Vaccinated and adjuvant-inoculated animals showed an increase in aggressive interactions ($p<0.001$) and stereotypies ($p<0.001$) and a decrease in affiliative interactions ($p<0.001$) when compared with the control group. Differences were more marked with higher number of doses applied. Repetitive inoculation of aluminum-hydroxide only or combined into commercial vaccines to experimental lambs induces highly persistent injection site granulomas, accumulation of aluminum in distant tissues and changes in the inter-individual interaction patterns.

AUTO1-0223
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

CEREBRAL 18F-FDG PET FOR DIAGNOSING ALUMINUM HYDROXIDE-INDUCED MACROPHAGIC MYOFASCIITIS

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Background

Macrophagic myofasciitis (MMF) is a condition observed in patients with abnormal long-term persisting aluminum hydroxide within body. A peculiar pattern of cerebral glucose hypometabolism involving occipito-temporal cortex and cerebellum was reported in patients with MMF. Aim was to generate and evaluate a support vector machine (SVM) procedure to classify patients between healthy or MMF 18F-FDG brain profiles.

Method

18F-FDG PET brain images of 119 patients with MMF and 64 healthy subjects were retrospectively analyzed. The whole-population was divided into two groups; a training set (100 MMF, 44 healthy subjects) and a testing set (19 MMF, 20 healthy subjects). Dimensionality reduction was performed using a t-map from statistical parametric mapping (SPM) and a SVM with a linear kernel was trained on the training set. To evaluate the performance of the SVM classifier, values of sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy (Acc) were calculated.

Results

The SPM12 analysis on the training set exhibited the already reported hypometabolism pattern involving occipito-temporal and fronto-parietal cortices, limbic system and cerebellum. The SVM procedure, based on the t-test mask generated from the training set, correctly classified MMF patients of the testing set with following Se, Sp, PPV, NPV and Acc: 89%, 85%, 85%, 89%, and 87%.

Conclusion

This original and individual approach including a SVM could help to classify patients between healthy or MMF metabolic brain profiles using

18F-FDG-PET. Machine learning algorithms are promising for computer-aided diagnosis but will need further validation in prospective cohorts

AUTO1-0810
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

ADVANCES IN OUR UNDERSTANDING OF IMMUNIZATION AND VACCINES FOR PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is a chronic, complex, multi-factorial, systemic autoimmune disease, in which immune system impairment and dysfunction result by virtue of the disease itself as well as by the effects of treatment modalities employed. Immune dysregulations occur including complement system dysfunction. Infectious agents are known to complicate the disease course in 25-45% of SLE patients. In this oral communication, a discussion of the immunogenicity and safety of viral and bacterial vaccinations in SLE subjects will be envisaged. For this purpose, we have carried out a comprehensive literature search, mining different scholarly electronic databases, including ISI Web of Science (WoS), Scopus, MEDLINE/PubMed, Google-Scholar, Directory of Open Access Journals (DOAJ), EbscoHOST, Scirus, Science Direct, Cochrane Library and ProQuest. Proper string made up of a key-words including 'SLE', 'vaccination', 'safety' and 'efficacy' has been used. Collecting the available evidence, we can maintain that vaccination in SLE patients is proven to be immunogenic. Concerns regarding vaccine safety are postulated, yet no direct relationship between vaccination and disease exacerbation were established. While live virus vaccines are generally contraindicated in immunosuppressive states, generally live attenuated vaccinations are recommended in SLE patients on a case-to-case basis. In SLE patients, clinical parameters such as vaccination during disease exacerbations have not been intensively studied and therefore while apparently safe, vaccination is generally recommended while disease is quiescent.

AUTO1-1068
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

EXPERIMENTAL EVALUATION OF THE TOXICOKINETICS OF ALUMINIUM-BASED ADJUVANTS: WHAT IS WRONG WITH THE REFERENCE STUDIES?

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The hypothesis suggesting that aluminum (Al)-based adjuvants are innocuous is based on 3 toxicokinetic reference studies that we examined in the light of current scientific knowledge.
The single experimental study was carried out using isotopic 26Al (Flarend et al., 1997). This study ignored adjuvant uptake by cells and was conducted over a short period of time, using only 2 rabbits per adjuvant. At the endpoint, Al urinary elimination accounted for 6% for Al hydroxide and 22% for Al phosphate, which is incompatible with rapid urinary elimination of vaccine-derived Al. Then two theoretical studies have evaluated the potential risk of vaccine Al in infants, by reference to an oral « minimal risk level » (MRL) extrapolated from animal studies. Keith et al. 2002 used a high MRL (2 mg/kg/d), an erroneous model of 100% immediate absorption of vaccine Al, and did not consider renal and blood-brain barrier immaturity. Mitkus et al. (2011) only considered solubilized Al, with erroneous calculations of absorption duration. The used MRL was both inappropriate (oral Al vs. injected adjuvant) and still too high (1 mg/kg/d) regarding recent animal studies. Indeed we recently observed a non-linear dose-response using Al hydroxide on mice, suggesting that the view that Al adjuvant neurotoxicity and biopersistence obeys "the dose makes the poison" rule of classical chemical toxicity appears overly simplistic. Thus analyze of reference studies and recent experimental data both strongly suggest that novel studies of Al adjuvants toxicokinetics are needed to ensure their safety and restore population confidence in Al-containing vaccines.

AUTO1-0706
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

CARDIAC ARREST FOLLOWING HPV VACCINATION

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The development of vaccines has proven to be a successful and cost-effective for global human health, and they represent an essential part of preventive modern medicine.
It is obvious that vaccines are administered to millions of people worldwide, and that not everyone develops serious adverse manifestations. Hence, clearly there are some prior susceptibilities that make some people more at risk of experiencing an adverse reaction to vaccination than others.
There are three HPV vaccines administered as of date: the bivalent Cervarix vaccine, the quadrivalent Gardasil vaccine and the newly introduced 9-valent vaccine. The vaccine is composed of virus-like particles of the L1 major capsid proteins of different HPV serotypes. First launched in 2006, the aim was to substantially reduce the burden associated with HPV-related neoplasms. And indeed, the vaccine has been found to be effective, providing a long-lasting protection against HPV infection and premalignant lesions.
There appears to be a fine balance between the efficacy of vaccines and their potential toxicity. This is because the same mechanisms that drive the immune-stimulatory effect of vaccines have the capacity to provoke a variety of autoimmune adverse reactions.
In the current literature, there are numerous cases substantiating the link between adverse auto-immune reactions and HPV vaccines. Herein we present a case report of a 20 years-old young adult who developed fatal arrhythmia and cardiac arrest following the administration of the HPV vaccine.

AUTO1-1069
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

NEURODEVELOPMENTAL TOXICITY OF VACCINES IN A RODENT MODE

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Throughout neural development, the immune system plays integral roles by affecting neurogenesis, synaptogenesis, neuronal migration, and axon guidance. These functions for immune molecules suggest that perinatal immunotoxic insults can also mediate pathological responses in neurodevelopmental disorders, including autism spectrum disorder (ASD). Although immune challenges induced by vaccination have been suggested to cause autoimmune and inflammatory conditions (i.e., “ASIA”), it is often assumed that vaccine-induced immune stimulation does not affect brain development. Moreover, despite the fact that many vaccines contain constituents, such as aluminum, formalin and no declared inorganic contaminations, which have been associated with adverse neurological and immune outcomes, the entire pediatric vaccination schedule has never been tested for neurodevelopmental toxicity outcomes.
The present study aims at evaluating the effects of pediatric vaccination on brain development and neuromotor behaviour using a mouse model system.
In total 16 litters of C57BL/6J mice were divided into 4 experimental groups: control, mice injected with mouse weight equivalent dose of the current U.S. pediatric vaccination schedule, mice injected with triple doses of the vaccines, and mice injected with aluminum phosphate adjuvant in the amount found in the vaccination schedule. Animals were assessed for reflex development, neuromotor ability and ASD-related neurobehavioural abnormalities (NBAs), including impaired social interactions, anxiety, and cognitive function.
Our preliminary data show abnormal repetitive behaviors (barbering) and NBAs, such as decreased preference for social novelty in a social interaction test and altered anxiety behaviour in a light-dark box test in the treatment groups when compared to controls. Mice will be euthanized and these behavioral alternations will be further examined by biological and histological analysis.

AUTO1-0427
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

SUSPECTED ADVERSE EFFECTS AFTER HUMAN PAPILLOMAVIRUS VACCINATION: A TEMPORAL RELATIONSHIP

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In Japan, after receiving human papillomavirus (HPV) vaccination, a significant number of adolescent girls experience various symptoms, the vast majority of which have been ascribed to chronic regional pain syndrome (CRPS), orthostatic intolerance, and/or cognitive dysfunction. However, a causal link has not been established between HPV vaccination and the development of these symptoms. Between June 2013 and December 2016, we examined symptoms and objective findings in 163 female patients who had received HPV vaccination. We used newly defined diagnostic criteria for accurate inclusion of patients who experienced adverse symptoms after HPV vaccination. Consequently, 43 females were excluded. Among the remaining 120 patients, 30 were diagnosed as having definite vaccine-related symptoms, and 42 were diagnosed as probable. Among these 72 girls, the age at initial vaccination ranged from 11 to 19 years (average 13.6±1.6 years), the age at appearance of symptoms ranged from 12 to 20 years (average 14.4±1.7 years), and the incubation period after the first vaccine dose ranged from 1 to 1532 days (average 319.5±344.3 days). These 72 patients received the HPV vaccine between May 2010 and April 2013. The first affected girl developed symptoms in October 2010, and the last two affected girls developed them in October 2015. Over the previous 14 months, we have not seen any female patients who were freshly affected by these symptoms. Based on these sequential events, it is likely that HPV vaccination plays some role for the transiently high prevalence of the previously mentioned symptoms including CRPS and autonomic and cognitive dysfunctions. Additionally, I will present HLA genotypes of the affected girls, which is helpful for the understanding of the pathogenesis in this unexpected disorder after HPV vaccination.

AUTO1-0595
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

HPV VACCINATION SYNDROME. A NEW TRAGIC FIBROMYALGIA MODEL?

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Several independent investigators have described the onset of a chronic illness soon after HPV vaccination. This illness is characterized by headache, fatigue, widespread pain, dizziness and nausea, among other vexing symptoms. This cluster of symptoms has been dubbed “HPV vaccination syndrome”. Profound dysautonomia and small fiber neuropathy have been reported in these cases. In the largest published series of 45 girls with HPV vaccination syndrome, 53% of them fulfilled the ACR 2010 fibromyalgia diagnostic criteria.
Dysautonomia and small fiber neuropathy are frequent findings in fibromyalgia. Dorsal root ganglia sodium channels have been implicated in the pathogenesis of fibromyalgia’s neuropathic pain. Therapies used in fibromyalgia directed to restore autonomic nervous system resilience could theoretically help post-HPV vaccination cases. New sodium channel blockers are being developed. These new compounds could become effective analgesics. On the other hand, HPV vaccination syndrome severity and clear-cut inception could become a new tragic model for fibromyalgia dysautonomic-neuropathic nature.

AUTO1-0636
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

VISUALISING ALUMINIUM IN HUMAN BRAIN TISSUE IN AUTISM AND MULTIPLE SCLEROSIS

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Background

Human exposure to aluminium has frequently been implicated in disease progression and most notably in neurodegenerative conditions, including Alzheimer's disease. Toxicity of the metal ion *in vivo* occurs through myriad pathways, of which its inclusion as the most commonly used adjuvant in human vaccinations has been linked to autoimmunity (or autoinflammatory) syndrome induced by adjuvants (ASIA).

Method

Using the complementary methods of transversely heated graphite furnace atomic absorption spectroscopy (TH-GFAAS) and lumogallion fluorescence microscopy, we have investigated the total quantity of aluminium and its location within human brain tissue, across multiple disease states.

Results

Aluminium in brain tissues of donors diagnosed with genetically triggered or familial Alzheimer's disease revealed extremely high concentrations in excess of 10µg/g tissue dry wt. and predominantly, the extracellular deposition of the metal ion. More recently, we have reported on the distribution of aluminium in autism spectrum disorder (ASD). Interestingly, intracellular aluminium was observed predominantly in non-neuronal, glial-like cells. The study additionally revealed some of the highest aluminium concentrations yet recorded.

Conclusion

We are now focusing our efforts on analysing brain tissues from donors diagnosed with multiple sclerosis, to draw comparisons of the distribution of aluminium across these complex neurological disorders.

AUTO1-0596
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

HUMAN PAPILLOMA VIRUS AND LUPUS. THE VIRUS, THE VACCINE AND THE DISEASE (THE SIMILARITY BETWEEN HPV AND EBV).

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Purpose of review:
Systemic lupus erythematosus (SLE) is a well-known, wide-spread autoimmune disease, involving multiple organ systems, with a multifaceted, widely unmapped etiopathogenesis. Recently a new aspect of morbidity has been described among SLE patients: infection with human papilloma virus (HPV). We set out to review data regarding the intricate relationship between the two and attempt to determine whether HPV may pose as a contributing factor to the development of SLE.
Recent findings:
We relate to epidemiological, molecular and clinical data. We've found evidence in all these fields suggesting HPV to be involved in the pathogenesis of SLE: increased prevalence of HPV infection among SLE patients; vast molecular homology between viral peptides and human proteins associated with SLE; several reports of SLE development post HPV vaccination. Our findings suggest a possible involvement of HPV infection in the induction of SLE, via a mechanism of immune crossreaction due to molecular homology.
Summary:
We review clinical, epidemiological and molecular data suggesting involvement of HPV infection in the pathogenesis of SLE. We suggest these findings may justify the development of new HPV vaccines containing viral peptides which bear no homology to the human proteome, in order to avoid possible adverse immune crossreactivity.

AUTO1-0634
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

ELUCIDATING THE RELATIONSHIP BETWEEN THE CONCENTRATION OF ALUMINIUM SALTS USED IN VACCINES AND THE SUBSEQUENT EVENTS OCCURRING AT THE INJECTION SITE

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Background

Aluminium salts remain the most commonly used adjuvants in clinical vaccinations despite an increasing number of adverse reactions being observed in individuals inoculated with such formulations. While current FDA regulations permit the inclusion of no more than 850 µg/dose Al within these preparations, the scientific rationale behind the introduction of this limit remains poorly justified. This study aims to explore how the concentration of aluminium in vaccines influences the biological processes occurring at the site of injection.

Method

Sizing experiments were conducted using a combination of dynamic light scattering, size exclusion filtration and graphite furnace atomic absorption spectroscopy.

Results

The hydrodynamic size of adjuvanted model vaccines showed a strong linear dependency on the concentration of aluminium included within the preparations, which influenced both the cytotoxicity and uptake of the material in a model phagocytic cell line.

Conclusion

These experiments provide an initial basis for the refinement of the amount of aluminium used within clinical vaccines, which will improve the safety of these formulations without comprising their efficacy.

AUTO1-0424
VACCINES, ALUMINIUM ADJUVANTS AND AUTOIMMUNITY

THE EVIDENCE FOR THE ASIA SYNDROME -THE REGISTRY AND EPIDEMIOLOGICAL STUDIES

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Vaccine induced autoimmune reactions are not so common and, as such, difficult to capture, being often under-reported and under-represented in the extant scholarly literature. However, recent large cohort studies and meta-analyses have confirmed at least some of them, including Guillain-Barrè syndrome after influenza vaccination, immune thrombocytopenic purpura after measles, mumps and rubella vaccine, viscerotropic and neurotropic diseases after yellow fever immunization, neurological complications after oral poliovirus vaccine and smallpox immunization. "Autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) syndrome appears to be a valuable umbrella term to collect and describe clinical symptoms and reactions arising after vaccines/ /silicone/ and some mineral oil exposure. Thus, ASIA syndrome includes those clinical conditions in which the exposure to an adjuvant leads to an aberrant autoimmune response. However, the vaccine attributable risk appears to be low and, undoubtedly, the benefits offered from vaccinations or immunotherapies outweigh vaccine- and immunotherapy-related adverse events. On the other hand, the classical paradigm of the actual routine pharmacovigilance/vaccine vigilance system based on three stage-approach (namely, signal detection, development of a causality hypothesis, and testing of the causality hypothesis) is plagued by some limitations, in that it is not sufficient to understand suspected harms that are poorly defined and whose pathophysiology are multi-factorial and not completely understood. Furthermore, estimations of risk at the population level fail to acknowledge that vaccines/immunotherapies may cause harm in subgroups with specific, individual-level risk factors for adverse events following immunization. The establishment of an international "ASIA syndrome registry" may contribute to an increased awareness of ASIA syndrome and help physicians to identify patients at a greater risk of autoimmune diseases following the exposure to vaccines and other adjuvants, providing a useful tool to systematize this rare condition.

AUTO1-0877
70th MOSAIC OF AUTOIMMUNITY

ROLE OF GERMINAL CENTERS IN PRIMARY SJOGREN'S SYNDROME: CXCL13 AND CXCL12 FUNCTION AND ASSOCIATION WITH HISTOLOGICAL, CLINICAL AND LABORATORY FEATURES

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Background

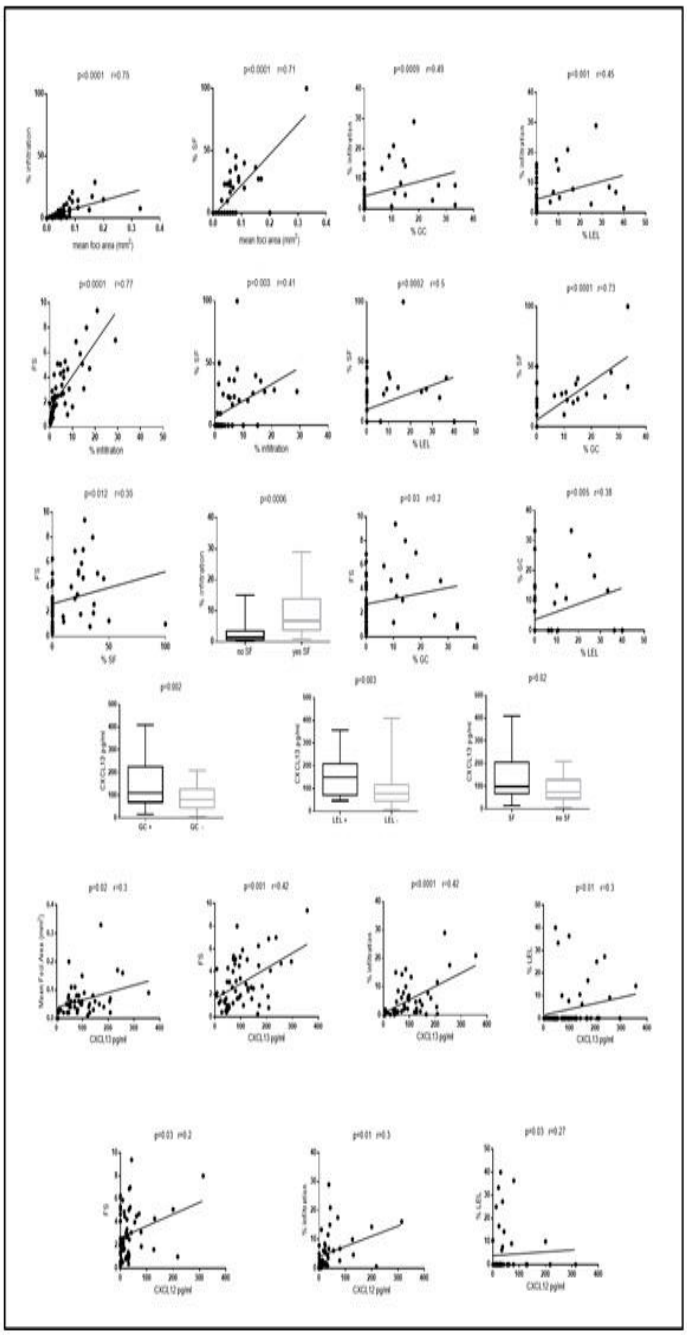
In primary Sjogren's Syndrome (pSS) salivary glands, several chemokines are able to organize the germinal center (GCs). Aim of this study is to investigate CXCL13 and CXCL12 serum and tissue expression and to find any association with clinical, histological and laboratory features.

Method

Both serum and paraffin embedded minor salivary glands (MSG) were collected from pSS patients. CXCL13 and CXCL12 were evaluated by ELISA and MSG stained in H&E and IHC (T/B lymphocytes and FDC detection). Focus score (FS), mean foci area, percentage of infiltration (%i), presence of segregated foci (SF), GCs and lymphoepiteliallesions (LEL) were evaluated. On frozen MSG GCs microdissection was performed (human tonsils as control). RNA extraction, cDNA reverse transcription and qPCR were executed.

Results

PATIENTS	SERUM ANALYSIS	HISTOLOGICAL ANALYSIS
Demographic features	Mean±SD	Mean±SD
Mean age	54.6±12.5	54.8 ±12.5
Mean age at diagnosis	51.7±12.2	52.1 ±12.2
Laboratory/clinical features	Number/70 (%)	Number/50 (%)
ANA	50/70 (71.4)	37/50 (74)
Anti-Ro/SSA antibodies	28/70 (40)	16/50 (32)
Anti-La/SSB antibodies	20/70 (28.5)	13/50 (26)
Rheumatoid Factor	20/70 (28.5)	12/50 (24)
Hypergammaglobulinaemia	23/70 (32.8)	15/50 (30)
Cryoglobulins	2/70 (2.8)	2/50 (4)
Monoclonal component	8/70 (11.4)	8/50 (16)
Hypocomplementaemia	9/70 (12.8)	5/50 (10)
Leucopenia	12/70 (17.1)	5/50 (10)
Xerostomia	61 /70 (87.1)	46/50 (92)
Xerophtalmia	60/70 (85.7)	46/50 (92)
Gland swelling	24/70 (34.2)	15/50 (30)
Lymphoma	8/70 (11.4)	0 (0)



Seventy pSS and eleven healthy controls (HC) were enrolled and 50 MSG collected (*table 1*). Histologic results are in *image*. Mean CXCL13 and CXCL12 were higher in pSS [(124.12±119.73 pg/ml vs 8.9±15.4 pg/ml (p=0.001) and 34.6±54.2 pg/ml vs 2.5±8.3 pg/ml (p=0.05), respectively]. CXCL13 was associated with anti-SSA (p=0.001) and anti-SSB antibodies (p=0.01), RF (p=0.0006), hypergammaglobulinemia (p=0.006), low complement (p=0.0006), leukopenia (p=0.03). CXCL13 was higher in lymphoma patients (p=0.009) and associated with histologic parameters (*image*). CXCL12 was higher in GCs from MSG compared to tonsil (p<0.0001).

Conclusion

Our results suggest the utility to include in the histologic evaluation also parameters other than the FS. CXCL13 proved to be a serum biomarker able to stratify pSS patients. The evidence of a higher CXCL12 expression in GCs from pSS, suggests its possible role in driving lymphocytes B proliferation.

AUTO1-0944
70th MOSAIC OF AUTOIMMUNITY

THE MICROBIOME IN AUTOIMMUNE DISEASES

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The human body is densely populated by commensal and symbiotic microbes, with the majority of the constituent microorganisms being bacteria. These microbes occupy different habitats such as gut, skin, vagina, oral. Not only the types and abundance of microbes are different in different organs, but also these may differ in different individuals. The genome of these microorganism and their ecosystem constitute to form a microbiome. Factors such as diet, environment, host genetics, mode of delivery may be the reason behind the wide microbial diversity1,2. The presence of the microbiome and the microbial products (i.e. butyrate, PSA, SCAFs) can regulate the development and function of the immune system in the host 2. Although the commensals reside mainly at the mucosa, the effect of microbiota on the immune system can be both local at the and systemic 3. In fact, there is "a close dialogue" between bacteria and host immune system, through pattern recognition such as Toll-like receptor (TLRs) present on the membrane of the immune and epithelial cells4.The interaction between TLRs and molecular models associated with microbes (MAMPS) expressed by the resident microbiota or molecular models associated with pathogens (PAMPS), induce several intracellular signal transduction cascades, resulting in the production of cytokines, chemokines and transcription factors5. A number of studies performed on human microbiome have revealed that the composition present in healthy and diseased individuals are distinct. Alteration of the microbiome (dysbiosis) can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens. The dysbiosis can induce the lost of tolerance in immune system and thus activation of the immune system cells2. It's now clear that alteration of the microbiome in subject with certain genetic background or exposed to environmental factors, can underlay of the pathogenesis of the autoimmune diseases . In this rispect, an alteration of the intestinal flora (lower Firmicutes/Bacteroidetes ratio) is described in patients whit lupus 6 Moreover, changes in the gut commensal and periodontal infection disease are proposed as important factors for the pathogenesis of rheumatoid arthritis 7,8. Anyway, other autoimmune diseases (i.e. systemic sclerosis, Sjogren's syndrome, antiphospholipid syndrome, type1 diabetes mellitus and multiple sclerosis) exhibit an imbalance of the gut or oral flora9. On the other hand, many efforts have been made to understand how we can manipulation the human microbiome to restore an imbalance of the commensal bacteria. The microbial supplements (probiotics, diet or prebiotics), already know in paediatric and general medicine, have been shown to decrease inflammatory activity restoring the gut flora 10. Indeed, in mice model of lupus nephritis, (MRL/lpr), the administration of Lactobacillus sp have shown to improve renal function (by decreasing IL-6 and increasing IL-10 in the gut) other than intestinal permeability. Moreover, a decrease of the circulant IgG2a level, a major immune deposit in the kidney, wad found 11. The faecal transplantation (FMT), the process of transplantation of fecal bacteria from a healthy individual into a recipient, has gained increasing prominence in the last years. FMT seems to be highly effective in treating recurrent C. difficile in adults. Recently, some authors suggest that FMT may reveal beneficial results in treatment of autoimmune and neuropsychiatric disorders 12. Nevertheless, the role of the microbiome in autoimmune disease is not completely understood. Further studies will be necessary to clarify the importance of the commensal microorganisms.

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AUTO1-0904
70th MOSAIC OF AUTOIMMUNITY

STUDY OF SLEEP DISORDERS, DEPRESSION AND RELATED FACTORS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS.

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Background

Patients with systemic lupus erythematosus (SLE) have neuropsychiatric manifestations that interfere with their quality of life, social relationships and productivity. Sleep disorders are present in more than half of patients with SLE and are associated with higher activity index, fatigue, depression and disability.
To evaluate the quality of sleep in patients with SLE and compare it with healthy subjects and to evaluate the link between sleep disorders and clinical manifestations, laboratory, activity of the disease and accrued damage.

Method

Descriptive, case-control study.

Patients ≥ 18 ys with SLE (ACR 1997) consecutively from January to July 2017, that they would have been able understand the Informed Consent and questionnaires.

We studied clinical and demographic variables, including SLEDAI and SLICC. We determine: psychiatric, neurological and sleep disorders.

Controls: healthy subjects ≥ 18 ys who accept to answer questionnaires.

Sleep disorder was assessed by self-questionnaires: severity of insomnia (ISI), quality of sleep (PSQI), depression by BECK, FACIT scale, HAQ.

Results

We included 51 cases (mean age 39.6 ± 12.9, 92% women) and 49 controls (mean age 41.8 ± 13.0, 88% women).

Variables	SLE n = 51	Controls n = 49	p
SI score **With Insomnia n (%)**	35 (68.62)	15 (30.61)	0.00
PSQI Score, mean (DS), n (%) **Bad sleeper (PSQI > 5), n (%)**	8.72 ± 4.28 36 (70.59	5.8 ± 3.76 24 (48.98)	0.00 0.02
PSQI Quality of dream Good + Quite good, n (%) Bad + Quite bad, n (%)	 26 (51) 25 (49)	 39 (79.6) 10 (20.4)	 0.04 0.04
PSQI Dream Latency ≤ 15 minutes, n (%) 16-60 minutes, n (%) > 60 minutes, n (%)	 9 (17.65) 32 (62.7) 10 (19.61)	 25 (51.02) 22 (44.9) 2 (4.08)	 0.00 0.05 0.01
PSQI Dream Latency > 30 minutes **Never in the last month, n (%)**	9 (17.27)	24 (48.98)	0.00
PSQI Sleep < 5 hours, n (%)	12 (23.53)	2 (4.08)	0.00
PSQI Dream efficacy <85%, n (%)	28 (54.90)	19 (38.78)	0.07
PSQI Wake up at night ≥ 3 week, n (%)	21 (41.18)	9 (18.37)	0.01
PSQI Pain ≥ 3 per week, n (%)	12 (23.53)	1 (2.04)	0.00
PSQI Sleeping treatments ≥ 3 weeks, n (%)	10 (19.31)	7 (14.29)	0.33
BECK n (%)	17 (33.33%)	2 (4.08)	0.00
FACIT mean ± DS	34.85 ± 11.08	39.85 ± 8.76	0.01
HAQ ≥ 0.75, n (%) **HAQ ≥ 1.5, n (%)**	11 (21.57) 5 (9.80)	0 0	0.00 0.03

SLE Group	With Insomnia n=35	Without Insomnia n=16	p
Body mass index, mean ± DS	28.55 ± 4.2	25.90 ± 5.23	0.08
Steroids mg/day, mean ± DS	11.82 ± 11.89	4.81 ± 2.85	0.02
≥ 3 Comorbidities #, mean (%)	11 (31.43)	1 (6.25)	0.04
BECK Score: depresión, n (%)	17 (48.57)	0	0.00
FACIT Score, mean ± DS	31.46 ± 11.13	42.25 ± 6.59	0.00
HAQ, media ± DS	0.50 ± 0.56	0.13 ± 0.2	0.00

Conclusion

Patients with SLE had more insomnia and alterations in sleep quality compared with controls.In the SLE with Insomnia group we found higher body mass index coinciding with the higher dose of steroids, as well as depression, fatigue and functional disability. There were not significance differences in patient with/without insomnia in: mean age, schooling < 12 years, ethnicity, socioeconomic status, smoking alcoholism, sedentary lifestyle, SLE symptoms, SLICC, SLEDAI, vitamin D, immunosuppressive therapy.

AUTO1-0548
70th MOSAIC OF AUTOIMMUNITY

USEFULNESS OF RHEUMATOID FACTOR AS AN IMMUNOLOGICAL AND PROGNOSTIC MARKER IN PSS PATIENTS

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Background

The rheumatoid factor (RF) is present in numerous autoimmune disorders, although its role in many of them remains a subject of research.The study assess the RF role as an immunological and prognostic factor in the primary Sjögren's Syndrome (pSS).

Method

75 pSS patients (mean age 50,03 ± 15,1), 65 (87%) females and 10 (13%) males. WBC, CRP, RF, ESR, gammaglobulins,C4, C3 component of complement, cryoglobulins, ANA, anti-SS-A and anti-SS-B antibodies were determined. The disease activity assessed with ESSDAI. Minor salivary gland biopsy (focus score and immunochemistry) was conducted. Results were analyzed with U Mann-Whitney (continuous variables) tests, correlations between quantitative variables assessed with the Spearman correlation coefficient with statistical significance set at $p<0.05$. The approval of the Bioethics Committee was obtained.

Results

Two subgroups: I-RF(+) (61%) and II-RF(-) (39%) were established, with lower WBC (p=0,012) and higher ESR (p=0,016), gammaglobulin conncentration (p=0,007) in group I. Conjunctivitis sicca was more severe in group I. There was positive correlation between RF and ANA (rho=0,530), anti-SS-A, anti- SS-B antibodies (rho=0,448; rho=0,397 respectively) and higher disease activity (ESSDAI> 5; p=0.071). RF correlated negatively with WBC (rho = -0,374). RF didn't correlate with serum concentrations of BAFF, APRIL, CRP, and C3, C4 and with CD19 +, CD3 +, CD4 +, CD 21+, CD35 +.

Conclusion

RF should be considered as a prognostic, but not diagnostic, factor in patients with pSS, as it is associated with more severe disease course (sicca eye symptoms, ESSDAI) and parameters (production of gammaglobulins, ANA, anti SS-A, anti-SS-B autoantibodies) indicating increased B cell activity.

AUTO1-1067
70th MOSAIC OF AUTOIMMUNITY

SHOENFELD´S SYNDROME: A CASE REPORT OF MCTD AND CFS RELATED TO CHRONIC EXPOSURE TO SILICONE OIL

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Increasing evidence support that medical silicone, mainly in the form of breast implants, may trigger autoimmunity, through a process called siliconosis, and lead to Shoenfeld´s/ASIA Syndrome. The authors, report an unusual case of Mixed Connective-Tissue Disease (MCTD) and Chronic Fatigue Syndrome (CFS) following lip augmentation with silicone oil filler.
A 64 year old woman, with a relevant past history of lip augmentation with silicone oil in 2001 for aesthetic purposes, and a diagnose of PBC in 2011, was referred to the rheumatologic department in January 2016, with complaints of lip swelling (image 1), feverish evening temperature, fatigue, generalize waning pains, swelling of the interphalangeal joints, dry cough, dryness of mouth and eyes, cognitive impairment, depressive symptoms and fatigue. There were no complaints of Raynaud phenomena, mouth ulcers or skin rash. Further study revealed one episode of bilateral uveitis reported by her ophthalmologist 3 years ago. Blood tests for autoimmunity revealed an elevated ANA titer 1/640, a positive AMA and a borderline titer of ACE. Anti-dsDNA, sm, SSA, SSB and ANCA were negative. Her chest X-Ray showed diffuse interstitial bilateral lung infiltrates. CT scan of her lungs showed mediastinal lymphadenopathy. Lung function tests were compatible with mild obstructive pattern that could be related to a lifelong exposure to tobacco. She had a mediastinal lymph node biopsy demonstrating infiltrates of multiple nucleated histiocytes and granulomas consistent with sarcoid-like lesions (image 2). Treatment with systemic corticosteroids was started with clinical improvement. The patient was considered to have MCTD associated with sicca syndrome and CFS, because of chronic exposure to silicone oil. She fulfilled the criteria for ASIA Syndrome. Histological analysis of lymph nodes and interstitial changes were discussed in the differential diagnosis of sarcoidosis vs siliconosis. PBC was possibly related to ASIA Syndrome.

Image 1

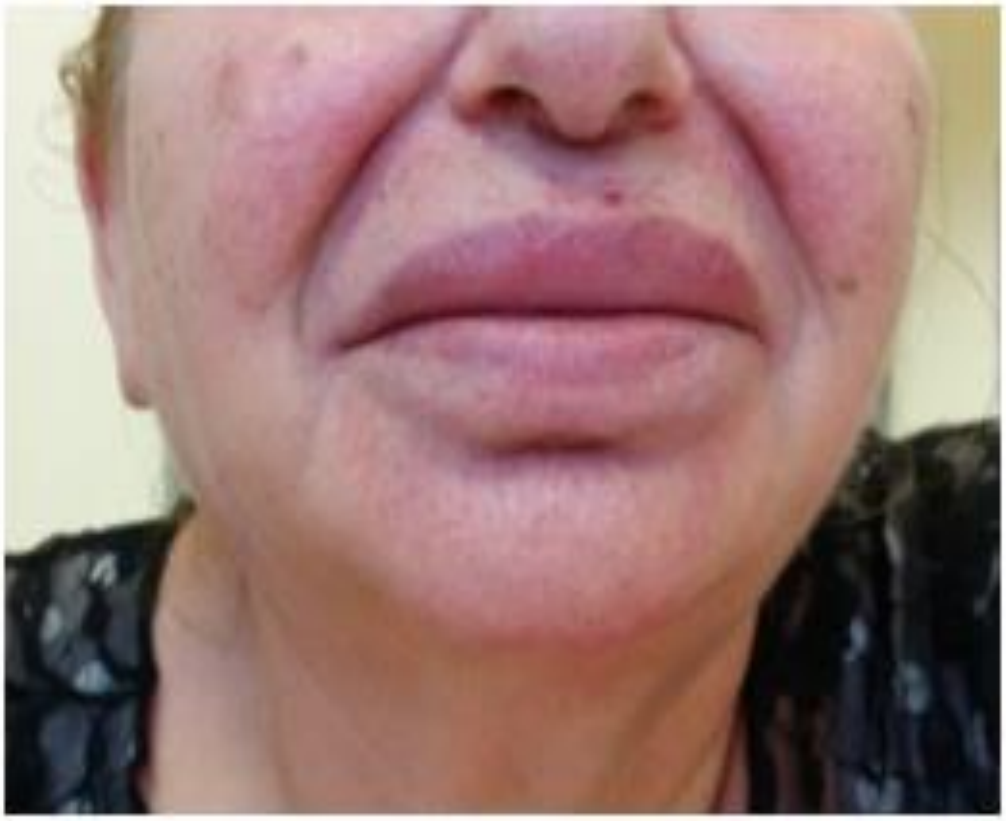
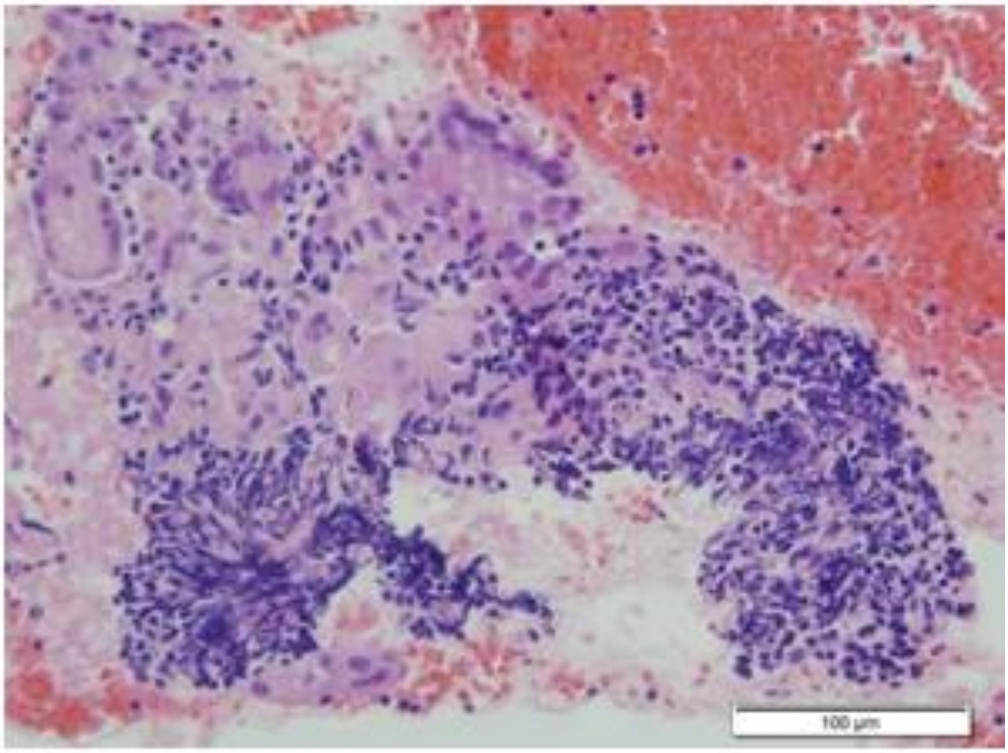


Image 2



multinucleated giant cells containing non specified cytoplasmatic inclusions and rom of lymphocytic inflammation in a sarcoid-like reaction (hematoxycilin and eosin x 400)

AUTO1-0933
70th MOSAIC OF AUTOIMMUNITY

HYPERFERRITINEMIC SYNDROME, WHERE DO WE STAND

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Background

In 2013 we described the “Hyperferritinemic Syndrome” where we proposed that the exceptionally high ferritin levels observed in four clinical conditions (macrophage activation syndrome (MAS), adult onset Still’s disease (AOSD), catastrophic antiphospholipid syndrome and septic shock) where not just the product of the inflammation but rather contribute to the development of a cytokine storm. Our proposed hypothesis challenged the *status quo* and raised the question of whether ferritin is an innocent product of inflammation or if, itself, has a pathogenic role. Since this provocative idea was raised in the scientific community, what has changed?

Method

Several studies have been conducted focusing on the possible pathogenic role of ferritin, and our paper has been cited innumerous times, revealing a raising interest in this subject.

Results

Studies have come out looking for the implications of ferritin (H and L) in some of those diseases. Emerging evidence corroborates our viewpoint. In fact, tissue H-ferritin has been found to correlate with clinical features, in patients with MAS as well as in AOSD, suggesting ferritin as a possible biomarker of severity, which could aid in early disease diagnosis, as well as in monitoring response to treatment modalities. Other papers support that ferritin, mainly the peptide H-ferritin, has a wide array of functions, including a pathogenic role, being not simply the product of inflammation.

Conclusion

We continue to reinforce that the concept of understanding the mechanism of a possible role of hyperferritinemia in the pathogenesis of these diseases would allow for the development of more targeted therapy.

AUTO1-0843
70th MOSAIC OF AUTOIMMUNITY

THE ROLE OF STRESS IN THE MOSAIC OF AUTOIMMUNITY: DE-STRESS TO PROTECT YOUR BODY

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Stress is defined as the pscyophysiological reaction in which the steady state is disturbed or threatened. Stress is not always perceived as a negative response. Stress results when environmental demands exceed an individuals' adaptive capacities. Autoimmune diseases are heterogeneous group of chronic diseases which occur secondary to loss of self antigen tolerance. The etiopathogenesis of autoimmune disease is uncertain. Genetic factors as well as environmental factors appear to interplay, leading to a cascade of events resulting in disease onset. Stress has been postulated to play a role in disease onset in the genetically susceptible patients. During the stress response, catecholamines and glucocorticoids are released from locus coeruleus and adrenal gland. These biomolecules exert control over various immune cells in the innate and adaptive arms of the immune system, thereby altering the cytokine profile released. The increase of IL-4 promotes T-helper 2 (Th2) cell differentiation, while the decrease in IL-12 and the increased IL-10 production reduce the number of T-helper 1 (Th1) cells.. The relationship between stress and autoimmune diseases is intricate. Stress has been shown to be associated with disease onset, and disease exacerbations in rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, Graves' disease as well as other autoimmune conditions. In certain conditions such as psoriasis, stress has been implicated in delaying lesion clearance upon the application of standard treatment regimes. Finally, psychological therapy and cognitive behavioral therapy aimed to reduce stress levels was shown to be effective in influencing better outcomes in many autoimmune diseases. The purpose of this paper is to closer inspect the clinical evidence regarding the role of stress on influencing the various aspects of disease entities.

AUTO1-0177
70th MOSAIC OF AUTOIMMUNITY

BORDERLINE POSITIVE ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)-PR3/MPO DETECTION IN A LARGE COHORT TERTIARY CENTER: LESSONS LEARNT FROM A REAL-LIFE EXPERIENCE

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Background

Enzyme-linked immunosorbent assay **(**ELISA) and indirect immunofluorescence (IIF) are the best strategies for anti-neutrophil cytoplasmic antibodies (ANCA) detection. In a minority of subjects, ELISA-based ANCA testing may result in a borderline positive titre. Therefore, we assessed the clinical significance of such result.

Method

This is a retrospective study, which included all subjects screened for ANCA subtypes (myeloperoxidase/MPO or proteinase-3/PR3) with subsequent identification of borderline positive results as determined by ELISA and retested using IIF. Demographic, clinical and laboratory data of subjects with a borderline positive ANCA test were extracted from their medical records.

Results

14,555 PR3/MPO-ANCA tests were performed by ELISA during the study period (2006-2016). Of the 14,555 PR3-ANCA antibody tests that were performed, 94 were borderline positive (titre 0.9-1.1), and of 14,555 MPO-ANCA antibody tests, 43 were borderline positive (titre 0.9-1.1). Male-to-female ratio was 1:1.08 and the mean age was 50.95±21.79 years. Four MPO-ANCA (9.30%) and eleven PR3-ANCA (11.70%) antibody borderline samples resulted positive on IIF testing. Subjects with borderline positive MPO-ANCA were found to have a poorer outcome in terms of mortality, renal failure and the need of undergoing dialysis. Mortality in patients with borderline positive MPO-ANCA was related to sepsis (50%), malignancy (40%), and 10% occurred due to respiratory failure.

Conclusion

Subjects with borderline positive MPO-ANCA and positive p-ANCA (IIF) seem to have a less favorable outcome. Physicians should be aware of these findings and possibly perform a closer follow-up and a routine screening for these subjects.

AUTO1-1066
70th MOSAIC OF AUTOIMMUNITY

GIANT CELL ARTERITIS AND INFLAMMATORY BOWEL DISEASE – IS THERE A CONNECTION? RESULTS FROM A POPULATION-BASED STUDY

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Background:
Giant cell arteritis (GCA) is an autoimmune disorder which primarily affects large vessels, whilst inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), mainly targets the gut. Co-existence of the two maladies has been reported sporadically in the literature, therefore the purpose of this study was to assess the authenticity of such an association in a large, cross-sectional study.
Methods:
Utilizing data derived from the Clalit Health Services' registry, the largest health maintenance organization in Israel, we compared the proportion of CD and UC in GCA patients with age- and gender-matched controls. Univariate analysis was performed using Chi-square and student t-test and a multivariate analysis was performed using a logistic regression model.
Results:
The study included 5,657 GCA patients and 28,298 age- and gender-matched controls. GCA patients had a significantly increased proportion of both CD and UC in comparison with controls (0.81% vs. 0.12 and 0.69% vs. 0.2%, p-value < 0.001, respectively). The strength of the association between GCA and IBD was negatively correlated with the patients' age; thus the association was most robust amongst younger patients aged 18-44 (OR=13.2). The association between GCA and IBD remained significant when evaluated independently of confounding factors (OR=2.367, p-value < 0.01, Table 1).
Conclusions:
The probability that GCA patients also suffer from IBD is increased in comparison with age- and gender-matched controls. Our findings indicate that this association is most prominent in younger patients (<70). Screening for IBD amongst GCA patients in this age group may be warranted.

Table 1 - Multivariate logistic regression of covariates associated with IBD

Characteristic		OR	CI	P
Age		0.99	0.98- 1	0.49
Gender (Female)		1.25	0.87- 1.84	0.22
BMI		0.95	0.92- 0.98	**0.007**
SES:				
Medium vs. Low		1.42	0.94- 2.1	0.1
High vs. Low		1.74	1.13- 2.69	**0.012**
GCA		2.36	1.71-3.27	**<0.001**

IBD: Inflammatory bowel disease; BMI: Body Mass Index, kg/m2;
SES: Socioeconomic status; GCA: Giant Cell Arteritis

AUTO1-1075
70th MOSAIC OF AUTOIMMUNITY

MORTALITY OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS ADMITTED TO THE INTENSIVE CARE UNIT

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Introduction:
Systemic Lupus Erythematosus (SLE) patients are usually admitted to the Intensive Care Unit (ICU) due to disease exacerbations, infections, or non-disease-related conditions. The aim of our study was to investigate the causes and outcomes of these admissions in order to identify factors associated with short-term mortality.
Methods:
This retrospective cohort study included 27 SLE patients admitted to the general ICU of the Sheba medical center between the years 2002 -2015. The outcome was measured by 30-day mortality and by The Acute Physiologic and Chronic Health Evaluation (APACHE) II score. The demographic, diagnostic, physiological and laboratory variables of survivors and non-survivors were compared using univariate and multivariate Cox regression analyses. A receiver operating characteristic (ROC) curve was plotted for significant variables to illustrate their diagnostic capabilities.
Results:
27 patients were admitted to the ICU (female: 21 [77%], mean age: 51.1±15.4 years). The mean APACHE II score and the 30-day mortality rate were 23.4±8.3 and 29.6%, respectively. Infections, especially lower respiratory tract infections, were the cause of 66.7% of the admissions and accounted for 87.5% of the mortalities. The APACHE II score, Gram negative infections and sepsis were significantly associated with 30-day mortality (p=0.033, p=0.022 and p=0.01, respectively). APACHE II score of 27 and above was the strongest predictor of mortality with a sensitivity and specificity of 83.3% and 84.2%, respectively (AUC=0.82 p=0.022).
Conclusion:
SLE patients admitted to the ICU with Gram negative infections, sepsis or an APACHE II score of 27 and above should be promptly identified and treated aggressively.

AUTO1-0851
ADVANCES IN THERAPY OF SLE

REVIEW ON THE ANTI-U1-RNP OCCURRENCE IN LUPUS PATIENTS

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[1]

The anti-U1-RNP are known as the “sine qua non” immune marker for the mixed connective tissue disease (MCTD) diagnosis. However, anti-U1-RNP antibodies occur in other connective tissue diseases, including systemic lupus erythematosus (SLE).
MCTD is recognized now as a distinct entity. Even if MCTD is known to include SLE-related clinical features, the current most used MCTD classification criteria (Alarcon-Segovia and Kahn criteria) and the last SLE criteria (SLICC 2012) have in common only the synovitis item.
In SLE cohorts like John Hopkins and LUMINA, prevalence of 25-30% was reported for the anti-RNP antibodies. Also, the last 2017 British guideline for the SLE management is recommending anti-RNP testing in lupus patients.
About 13% of the patients from the Euro-Lupus cohort were found to have anti-U1-RNP antibodies. This positivity seems to be higher in certain SLE sub-groups. Thus, prevalence of 64% and 67% was found in lupus patients with SLE-related PAH and SLE patients with nail fold capillaroscopy changes, respectively.
In SLE cases that do not fulfill the MCTD classification criteria, U1-RNP positivity is associated with clinical features frequently reported in MCTD patients, like Raynaud phenomenon, musculoskeletal and lung impairment or nail fold capillaroscopy. Therefore, SLE patients with anti-U1-RNP antibodies should be screened for rather rare but severe lupus involvements such as interstitial pulmonary involvement or pulmonary hypertension.
The use of more specific immune markers like 70 kDA anti-U1-RNP, anti-Sm-D or IgG/ IgM serotype of the anti-U1-RNP were proposed for discriminating between SLE and MCTD.

AUTO1-0159
ADVANCES IN THERAPY OF SLE

NAILFOLD CAPILLAROSCOPY IN SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL

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Background

Systemic lupus erythematosus (SLE) is a rheumatic disease with common vascular involvement. Nailfold capillaroscopic changes have been described in SLE. This study reviews the literature on capillaroscopic changes described in SLE and determines the significant correlations of capillaroscopic parameters with clinical and laboratory findings, including autoimmune parameters.

Method

A sensitive search was performed by two reviewers in three databases to identify all original research studies (written in English) in which SLE patients had capillaroscopy. All included articles underwent quality appraisal. Results were summarised according to density, dimensions, morphology, haemorrhages, semi-quantitative assessment, qualitative assessment and correlation of capillaroscopic changes with clinical and laboratory parameters.

Results

From the 198 articles captured, 40 articles were retained (figure 1). The following capillaroscopic parameters were significantly more prevalent in SLE patients compared to healthy controls: tortuous capillaries, abnormal morphology, haemorrhages, a higher nailfold capillaroscopic score, “non-specific patterns” and “scleroderma-like pattern” (table 1). Hairpin-shaped capillaries were significantly more prevalent in healthy controls. Concerning clinical and laboratory parameters there is evidence that the disease activity is correlated with capillaroscopic changes. Single studies show significant associations with frequent Raynaud attacks, gangrene, anti-SSA and 24-hours proteinuria (table 2).

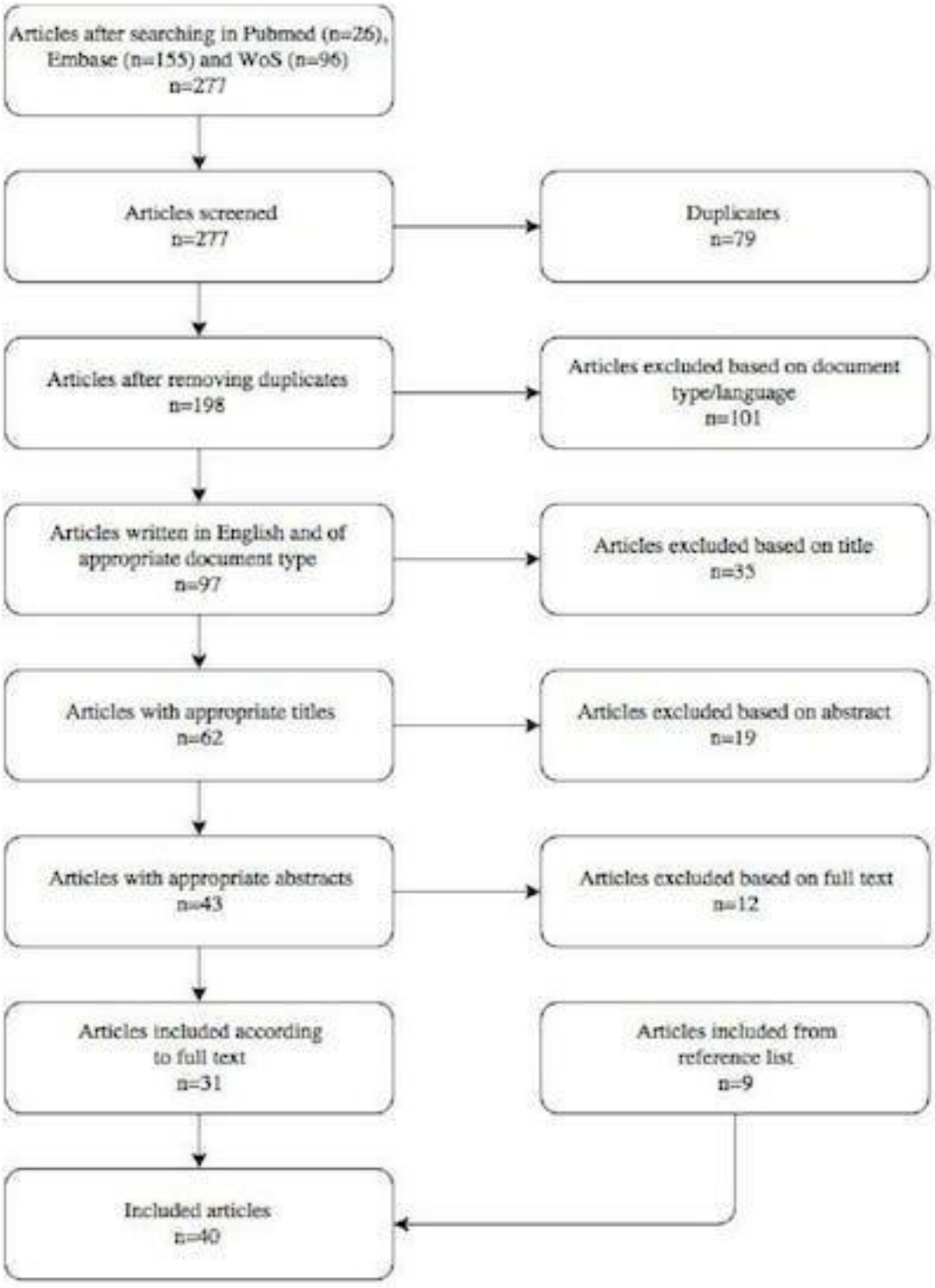

Figure 1: Flow chart literature selection

				Significant	Non-significant	Conclusion
Quantitative evaluation	Density	Mean density		4 studies	4 studies	Non-conclusive
		Avascularity		2 studies	0 studies	
	Dimensions	Diameter	Mean limb diameter	4 studies	2 studies	Non-conclusive
			Mean width	2 studies	2 studies	
			Enlarged width	4 studies	0 studies	
			Giant	1 study	0 studies	
		Length		3 studies	2 studies	Non-conclusive
	Morphology	Normal morphology	Hairpin shaped	2 studies	0 studies	Significant more hairpin morphology in healthy controls compared to SLE patients
			Tortuous	1 study	0 studies	Significant more tortuous capillaries in SLE patients compared to healthy controls
		Abnormal morphology		5 studies	0 studies	Significant more abnormal morphology in SLE patients compared to controls
	Haemorrhages			2 studies	0 studies	Significant more haemorrhages in SLE patients compared to controls
	NFC score			1 study	0 studies	Significant higher NFC score (based on density, dimension, morphology and haemorrhages) in SLE patients compared to controls
Qualitative evaluation	Other patterns			1 study	0 studies	Significant more presence of a pattern with tortuous and crossing, abnormal morphology (i.e. 'meandering'), enlarged capillaries and focal haemorrhages and more presence of a scleroderma-like pattern in SLE patients compared to controls

Table 1: Significance of capillaroscopic changes in SLE

Only studies reporting clear definitions on capillaroscopic changes and reporting a significance level of difference between SLE and healthy controls were considered in this table. When results were conclusive, the background was shaded.

			Significant	Non-significant	Conclusion
Clinical parameter	Raynaud's phenomenon	Positive vs negative	2 studies	7 studies	Non-conclusive
		Frequency of Raynaud's phenomenon	1 study	0 studies	Significantly more dilated capillaries in patients with frequent Raynaud attacks (> 1/week) compared to patients without Raynaud's phenomenon and compared to healthy controls
	Systemic organ involvement		4 studies	4 studies	Non-conclusive
	Disease duration		1 study	7 studies	Non-conclusive
	Disease activity[a]		8 studies	0 studies	Significant association of disease activity (SLEDAI/ECLAM/SLAM) with NFC score (7 studies), with abnormal morphology (i.e. 'meandering') (1 study) and with haemorrhages (1 study)
	Immunosuppressive agents		2 studies	1 study	Non-conclusive
	Nailfold bleedings/splinter haemorrhages		0 studies	1 study	No significant correlation between nailfold bleedings/splinter haemorrhages and capillary width
	Cutaneous manifestations		0 studies	4 studies	No significant correlation between cutaneous manifestations and nailfold capillaroscopic findings
	Gangrene		1 study	0 studies	Diameter of efferent and afferent limb is correlated with the presence of gangrene
Laboratory findings	Antibodies	Anti-cardiolipin	4 studies	2 studies	Non-conclusive
		Antinuclear antibodies	0 studies	4 studies	No significant correlation between antinuclear antibodies and capillaroscopic findings
		Anti-Sm	1 study	1 study	Non-conclusive
		Anti-Ro/Anti-SSA	1 study	1 study	Possible correlation between anti-SSA and lower density of capillaries
		Lupus anticoagulant	0 studies	1 study	No significant correlation between lupus anticoagulant and nailfold capillary abnormalities
		Anti-dsDNA	1 study	3 studies	Non-conclusive
		Anti-U1-RNP	3 studies	1 study	Non-conclusive
	Complement activity		0 studies	3 studies	No significant correlation between complement activity and capillaroscopic findings
	Hemoglobin		1 study	1 study	Non-conclusive
	Erythrocyte sedimentation rate		2 studies	2 studies	Non-conclusive
	24 hours proteinuria		1 study	0 studies	Significant negative correlation of abnormal morphology (i.e. 'meandering') with 24h proteinuria
	Leukocyte and thrombocyte count		0 studies	1 study	No significant correlation between leukocyte or thrombocyte count and capillaroscopic changes
	VEGF		5 studies	3 studies	Non-conclusive
	ET-1[b], sTM[b], sE-selectin[b]		1 study	2 studies	Non-conclusive

Table 2: Correlation of clinical parameters and laboratory findings with capillaroscopic changes

Only studies reporting clear definitions on capillaroscopic changes and reporting a significance level of difference between SLE and healthy controls were considered in this table. When results were conclusive, the background was shaded.

[a] SLEDAI (Systemic lupus erythematosus disease activity index), SLAM (Systemic Lupus Activity Measure), ECLAM (European Consensus Lupus Activity Measurements), NFC score (Nailfold capillaroscopic score)

[b] ET-1 (Endothelin-1), sTM (soluble thrombomodulin), sE-selectin (soluble E-selectin)

Conclusion

This first systematic review on capillaroscopy in SLE attests conclusive significant differences in morphology, haemorrhages, semi-quantitative assessment and qualitative assessment in SLE patients compared to healthy controls. Interestingly, results demonstrate an association of capillaroscopic changes with disease activity in SLE. Further large-scale research is ongoing through the EULAR study group on microcirculation in Rheumatic Diseases to further define its role in SLE.

AUTO1-0041
ADVANCES IN THERAPY OF SLE

MINIMAL RENAL AFFECTION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CHARACTERISTICS AND EVOLUTION

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Background

In SLE, indications of renal biopsy (RB) are deterioration of renal function and/or activity in sediment and/or proteinuria> 0.5g/24h or urine protein: creatinine ratio (P:C ratio)>0.5.There are patients who show data of "minimal renal involvement" (MRI) without indication of RB.Our objective is to determine if these patients present clinical and analytical characteristics that allow them to differentiate from patients with LN

Method

We reviewed 171 patients with SLE diagnosis,classifying them as MRI if they showed>3 occasions at least 1 year,proteinuria determinations = 0.3 g/24h or P:Cratio=0.3,ruling out urologic pathology. We have compared clinical and analytical variables of MRI vs LN at the time of SLE diagnosis,at renal involvement diagnosis and last visit

Results

We identified 38(18.7%)patients with MRI and 41(24%)patients with LN. At the time of SLE diagnosis, the MRI group had a lower titer of anti-DNAds(p=0.01),anti-Sm (p = 0.04),presence of lupus anticoagulant (p=0.01) and anticardiolipin IgG (p=0.01),less severe C3 hypocomplementemia (p=0.04),C4(p=0.04);and lower inflammatory parameters: ESR (p=0.01),CRP (p=0.02). At the diagnosis of the renal involvement, these results were confirmed(Table). In MRI patients, proteinuria appeared at an older age, with a higher evolution of SLE (p=0.02) and with absence of previous immunosuppressant therapy.After a mean follow-up of 10±6.6 years, no MRI patient presented a renal flare,maintaining stable the renal function

	LUPUS NEPHRITIS (n=41)	MINIMAL RENAL INVOLVEMENT (MRI) n=38	p
Sex (Female/Male)	30/11	29/3	0.05
Age (years)	38 ± 16	45 ± 17	0.07
Follow up time (years)	3.4 ± 5.5	5.8 ± 4	0.01
Creat (mg/dl)	1.3 ± 1.3	0.7 ± 0.2	0.02
URINE SEDIMENT • Negative • Hematuria • Leukocyturia • Changes in sediment	14 (35%) 3 (7,5%) 9 (22.5%) 14 (35%)	32 (100%)	NA
Proteinuria (mg/24h)	2044 ± 2700	266 ± 71.6	NA
(P:C ratio) (mg/gr)	1761,7 ±1446	232 ± 172	NA
HT (n, %)	3 (13%)	2 (6%)	0.6
DM2 (n, %)	2 (8%)	2 (6%)	0.7
DNA-crithuda	26 (74.3)	9 (37.5)	0.005
Anti-SSARO (IA)	13 (38.2%)	12 (38.7%)	0.5
Anti-La (IA)	8 (23.5%)	5 (16.1%)	0.3
Anti-RNP (IA)	13 (39.4%)	7 (24.1%)	0.1
Anti-Sm (IA)	13 (39.4%)	4 (14.3%)	0.002
C3 (mg/dl)	70±21.9	130±10	0.001
C4 (mg/dl)	16.1±3.9	26±10.8	0.001
C1q (mg/dl)	16.5±11	26±12.3	0.001
CH50 (U/mL)	34±5.3	71.0±15	0.001
Immunosuppressants • Micophenolic acid • Azathioprine • Hydroxyclorochine	15 (38.5%) 20% 13% 20%	25 (78,1%) 4% 88% 32%	0.001 0.1 0.001 0.003
Corticosteroids	19 (50%)	15 (46.9%)	0.4

Conclusion

Patients with MRI had a lower clinical and biological SLE activity,both at SLE diagnosis and at the diagnosis of renal involvement.No MRI patients presented a LN flare during the follow-up although it is difficult to know the role played by the immunosuppressant treatment

AUTO1-0121
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

ANA TESTING: IS STANDARDISATION OF PATTERN REPORTING POSSIBLE?

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Background

In 2009, the American College of Rheumatology (ACR) recommended use of immunofluorescence (IF) technique for anti-nuclear antibody (ANA) testing as the gold standard. Recently HEp-2 cells have been increasingly adopted as the universal standard substrate in practically all commercial ANA assays. ANA testing across different assays has resulted in the lack of standardisation at three levels: analysis, reading and reporting.

In 2014 members of the Autoantibody Standardization Committee assisted with the initiation of the **I**nternational **C**onsensus on **A**ntinuclear **A**ntibody **P**atterns (ICAP) with the aim to promote consensus in reporting patterns observed by IF on HEp-2 cells.

Method

To determine whether consensus was possible, UK NEQAS Immunology, Immunochemistry & Allergy (IIA) began to collate results in accordance with the ICAP reporting system. Results were submitted in two ways: from EQA samples that were circulated for testing and concurrent circulation of electronic images and questionnaire to try to eliminate variability in testing protocols and substrates utilised.

Results

Data suggests that although the ICAP system harmonises reporting to some extent, it is difficult to standardise methods for heterogeneous analytes. Difficulty seems to exist with speckled patterns, especially further differentiation between fine speckled and coarse speckled patterns. Similar results have been observed by Australian EQA providers (RCPAQAP), collaborators in this study.

Conclusion

Lack of standardisation of ANA slides makes comparison between assays and consistent reporting of ANA patterns problematic. ANA pattern matching is not enough to harmonise reporting and work needs to be undertaken with EQA providers to explore substrate related differences, performance and further education.

AUTO1-0599
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

A COHORT OF PATIENTS POSITIVE FOR ANTIBODIES FOR MYOSITIS AND MYOSITIS RELATED DISORDERS IN A LARGE TERITARY CENTER

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Background

Inflammatory myopathies are a clinically diverse group of diseases, in which the detection of particular autoantibodies may facilitate diagnosis and predict clinical course. The aim of this report is to summarize our experience with specific autoantibody testing in patients with inflammatory myopathies. Data were collected over the last decade in the Autoimmune Center of the Sheba Medical Center, a tertiary referral hospital.

Method

Data regarding patients' positive for autoantibodies against Jo-1, PL-7, PL-12, SRP, Mi-2, Ku, PM-Scl antigens were retrospectively collected. Patient demographics, clinical characteristics and mortality were recorded. Descriptive statistics (mean, standard deviation, frequency and percentage) were calculated.

Results

A total of 507 patients were tested for sclero-poly-synthetase antibodies, mainly due to myositis/myalgia or interstitial lung disease. Forty-three patients were positive for one or more antibodies, among them 23 patients (53.49%) had interstitial lung disease (ILD). Four patients were positive for anti-PL-7; three of them had ILD and Raynaud's phenomenon. Five patients were positive for anti-Ku, and four of them had both arthritis and Raynaud's phenomenon. Nine patients were positive for anti-Mi-2; among them six patients were given the diagnosis of dermatomyositis. Ten patients were positive for anti-SRP; of these six had cancers of various types.

Conclusion

Our results demonstrated the known relationship between anti-Mi-2 and dermatomyositis, between anti-Ku and Raynaud phenomenon, and between anti-PL-7 and ILD. Our data support a connection between anti-SRP and malignancy, which calls for further investigation.

AUTO1-0784
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

PREVALENCE OF ANA PATTERNS INCLUDING DFS70 IN SOUTH EAST CHINA: A CROSS SECTIONAL STUDY

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Background

To explore the prevalence of antinuclear antibody (ANA) patterns including anti-dense fine speckled 70 (DFS70) and their specificities in South east China.

Method

Two thousand three hundred and fifty-six consecutive sera from patients presenting to rheumatology clinic at Xiamen, China were screened at 1:100 using a novel HEp-2 DFS70 knockout (KO) indirect immunofluorescence substrate (HEp-2 ELITE/DFS70-KO, Trinity Biotech, Buffalo, NY). Serological pattern specificities were confirmed using immunoblot (Euroimmune AG, Lübeck, Germany).

Results

Out of the 387 cases (16.43%) that were positive for ANA patterns on the novel HEp-2 substrate, speckled and homogeneous were most frequently observed patterns with 236 (60.9%) and 59 (15.2%) cases respectively. Cytoplasmic (33, 8.5%), centromere (22, 5.7%), DFS70 (19, 4.9%), nucleolar (9, 2.3%), nuclear dots (8, 2.1%), nuclear envelope/membranous (1, 0.3%) were also reported. For all of the disease associated ANA patterns (excluding DFS70) reported, 209 (56.8%) out of 387 ANA positive cases were associated with an autoimmune diagnosis. In contrast, 16 (84.2%) of the 19 cases with DFS70 pattern were not associated with an autoimmune disease diagnosis.

Conclusion

The results mirror the prevalence rates reported in the literature in the rest of the world and show all major ANA patterns.
Majority (84.2%) of the 19 DFS70 positive cases (0.8% of the screening population or 4.9% of the ANA positive subset) identified were not associated with an autoimmune disease diagnosis.
Lack of association between DFS70 pattern and autoimmune disease diagnosis observed in this study is consistent with the published literature.

AUTO1-0255
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

ANTINUCLEAR ANTIBODIES (ANA) WORKUP IN THE CLINICAL PRACTICE: HOW MANY ANTIGENS SHOULD BE INCLUDED IN AUTOANTIBODY SCREENING?

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Background

Innovative powerful tools to detect ANA are emerging, thus questioning what is the best method for ANA screening. The aim of our study was to assess the impact on the real-life practice of ANA algorythms in two high-volume reference laboratories.

Method

We tested 320 consecutive samples (females 70.6%; mean age, females 48.8, 3-87, males 48, 1-88) with available clinical informations using 16 antigen EliA™ CTD screen (Thermofisher) and multiplex BioPlex®2200 ANA Screen (BioRad), associated with automated HEp-2 cell reading.

Results

Besides confirming some inter-laboratory variability in IIF reporting, we focused on discrepant results between IIF and solid-phase assays as well as on double-positive results, accounting for 13% and 17% of all tested samples, respectively. Among solid-phase positive samples, Ro-60 and Ro-52 were detectable in the great majority of cases associated with clinical significance, dsDNA positivity was found in half the patients, often not related to systemic rheumatic diseases, minor antigens being revealed in a few number of samples, always associated with connective tissue diseases.

Conclusion

In a complex case-mix population, with difficult to predict pre-test probability, solid-phase methods provide fundamental information and should be associated with IIF to maximize the diagnostic accuracy. Specific antigen testing can be an adequate screening test in most patients in the daily practice, if the correct kit is chosen and validated. By handling the current trend to automation, specialized autoimmunity laboratory must use all available tools in ANA testing, through a multi-step approach, starting from more common antigens and moving towards rare or esoteric specificities, though clinically relevant.

AUTO1-0649
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

VARIABILITY IN ICAP (INTERNATIONAL CONSENSUS ON ANA PATTERNS) PATTERN REPORTING IN TESTING FOR ANTINUCLEAR ANTIBODIES (ANA) BY INDIRECT IMMUNOFLUORESCENCE ASSAY (IFA)

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Background

ANA IFA pattern may guide clinical evaluation by directing specific antibody testing. ICAP has defined consensus ANA IFA patterns and the level of competency required to identify and interpret them.

Method

Laboratories participating in CAP proficiency testing for ANA in 2016 were queried to identify current practices in this interpretation and reporting.

Results

Of 638 performing ANA by IFA and reporting a pattern, nearly 100% reported nucleolar, 99% homogeneous and speckled, and 96% centromere, all competent-level ICAP patterns. Only 42% reported nuclear dots (competent-level). 53% reporting nucleolar pattern further described expert-level subpatterns. Of 519 reporting speckled patterns, only 29% reported dense fine speckles, a competent-level pattern reportedly found in normals. “Other” speckled was reported by 44%. 4% did not report speckled pattern at all. Of those reporting nuclear dots, 86% differentiated *many* nuclear dots and 84% *few* nuclear dots. Nuclear envelope (expert-level) was reported by 18%. Competent-level cytoplasmic patterns were reported: golgi 69%, mitochondrial 65%, speckles 30%, 17% rods and rings, reticular 12% and polar 10%. Expert-level cytoplasmic patterns were reported: spindle apparatus 59%, centriole 55%, mid body 45%, and lysosomal 32%. Only 54% used an internal fluorescence intensity standard.

Conclusion

Pattern reporting practice is variable. Cytoplasmic pattern reporting is limited, possibly reflecting a lack of consensus that cytoplasmic patterns should be reported in an “antinuclear” antibody test. Failure to use an internal fluorescence intensity standard by nearly half of the laboratories may increase inter-assay and inter-observer variation in the threshold for staining positivity and in titer determination.

AUTO1-0514
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

STUDY OF DEMAND CONTROL IN ANTINUCLEAR ANTIBODIES

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Background

Testing for antinuclear antibodies (ANA) plays an important role in the diagnosis of systemic autoimmune diseases (EAS). In all the related Clinical Practice Guidelines, the need to assess the clinical criteria for their request is insisted. Once the diagnosis is established, repeating positive ANA seems not to be useful. It would seem reasonable to retest those seronegative patients in case of continuing clinical suspicion and the course of the pathology. We wanted to know at what point we are in this determination in our laboratory, and as part of the management of the demand to establish a protocol for its realization.

Method

We reviewed all ANAs requested between 01.01.2016 and 31.12.2016 to our laboratory, through a consultation to our LIS.

Results

We performed 5954 ANA, which belonged to 5197 patients. We had performed 1368 repetitions, on 611 patients:

-357 First ANA: Negative

351 2nd Negatives

6 patients 2nd Positives: 4 error in the transcription of the result, one with a clinical change (justifiying the positive) and One with 2nd determination in the context of the infectious process.

-219 First ANA: Positive, they should not have been studied again.

Conclusion

Following CPG, we should not make second determinations to patients with previous positive ANA, and in case ANA negative only by contacting the laboratory for justification (only one case of seroconversion with clinical involvement in one year). The implementation of this protocol in the period of time studied would have saved 1367 ANA determinations with the cost and workload associated.

AUTO1-0756
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

PREVALENCE OF UNSPECIFIC INDIRECT IMMUNOFLUORESCENT PATTERNS IN HEALTHY PATIENTS: 5-YEAR REVISED CASUISTIC AS A REFERENCE CLINICAL LABORATORY CENTRE

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Background

Detection of anti-cellular antibodies of the ANA family is pivotal to the diagnosis of many autoimmune diseases. Moreover, ANA specific antibodies may present years before the appearance of overt disease, and for some conditions serological assays can provide useful information on the likelihood of clinical course or complications. Hence, the determination of ANA may enable the prediction, diagnosis and activity determination of certain autoimmune diseases.

Method

The authors present a prevalence of unspecific indirect immunofluorescent patterns in patients 5-year revised casuistic as a reference clinical laboratory center in autoimmune diseases diagnosis, focusing on the prevalence of unspecific indirect immunofluorescent patterns in patients with negative specific associated antibodies for the most prevalent autoimmune diseases.

Results

The recommended “gold standard” for ANA screening is IIFA on HEp-2 cells. IIFA entails substantial technical expertise and it is only as good as the laboratory that performs it. Another limitation of IIFA is its lack of specificity. Requests for these tests have risen remarkably and, depending on the population being studied, serum dilution, the cut-off used and other variables of this assay, up to 25% of sera from apparently healthy individuals can be ANA positive.

Conclusion

Noteworthy, in the general population, some individuals with a positive ANA test by IIFA do not have an autoimmune disease and are unlikely to develop one. As with every laboratory test, no test for ANA or for specific autoantibodies to nuclear antigens should be performed without a clinical evaluation that leads to a presumptive diagnosis.

AUTO1-0619
ANA DIAGNOSTICS (AUTOMATED EVALUATION OF IIFT AND MYOSITIS-SPECIFIC AUTOANTIBODIES)

CURRENT LABORATORY AND CLINICAL PRACTICES IN REPORTING AND INTERPRETING ANA PATTERNS IN BELGIUM.

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Background

The International Consensus on Antinuclear Antibody (ANA) Patterns (ICAP) has defined consensus ANA patterns and the level of competency required to identify them. This study aimed to evaluate current laboratory and clinical practices in reporting and interpreting ANA patterns.

Method

Questionnaires on ANA patterns (interrogating reporting, familiarity and clinical significance of patterns) were distributed to Belgian laboratories and rheumatologists.

Results

The response rate was 45.0%(49/109) for laboratories and 18.6%(41/220) for rheumatologists.

The patterns reported by most (>90%) laboratories and with a high familiarity (>90%) among rheumatologists include homogeneous, centromere, nucleolar, speckled and nuclear dots. Other patterns were less reported:

- · ICAP competent patterns: nuclear dense fine speckled(48.6%); cytoplasmic fibrillar(81.1%), cytoplasmic speckled(83.8%), reticular/AMA(73.0%), polar/golgi like(86.5%), rods and rings(51.4%)
- · ICAP expert patterns: nuclear fine(43.2%) and large/coarse(56.8%) speckled; multiple(64.9%), few(62.2%) nuclear dots; homogeneous(24.3%), clumpy(21.6%), punctate(16.2%) nucleolar; nuclear envelope(75.7%), smooth(10.8%) and punctate(8.1%) nuclear envelope; pleomorphic(73.0%), PCNA-like(40.5%), CENP-F-like(27.0%); cytoplasmic linear/actin(45,9%), filamentous/microtubules(45.9%), segmental(10.8%); discrete dots(32.4%), dense fine(29.7%) and fine(45.9%) speckled.

Clinicians considered the centromere(89.5%) pattern as clinically important, followed by homogeneous(57.9%) and, to a lesser extent, nucleolar(42.1%) and speckled(42.1%). Laboratory professionals also considered the anti-mitochondrial-like(75.0%) and nuclear dots(63.6%) pattern as clinically important. All other patterns

(including cytoplasmic and mitotic patterns) were considered of less (or no) clinical importance.

Antibody titers were reported by 87% of laboratories and clinically used by 73% of clinicians.

Clinicians and laboratory professionals (respectively 64.5% and 84.6%) considered a corresponding ANA pattern and specific ENA/dsDNA antibody identification as being most clinically relevant.

Conclusion

We documented how Belgian laboratory immunologists and rheumatologists value IIF patterns.

AUTO1-0985
ANCA AND VASCULITIS

PROTEINASE 3- AND MYELOPEROXIDASE- ANCA SPECIFICITY: USEFUL TOOL FOR THE SUBCLASSIFICATION OF SMALL VESSEL VASCULITIS

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a life-threatening, necrotizing inflammation of small/medium-sized blood vessels characterized by the presence of ANCA directed against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). The main syndromes are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA). Patients with GPA are predominantly PR3-ANCA-positive, whereas those with MPA and EGPA are predominantly MPO-ANCA-positive, although ANCA specificity overlaps only partially with these clinical syndromes. Several clinical and pathological classification systems exist that aim to define homogeneous groups among patients with AAV, however, considerable debate surrounds this classification. Existing classification sys¬tems have relied on combinations of different clinical, radiographic and histological findings, but have not included ANCA specificity. Accumulating evidence suggests that ANCA specificity could be better than clinical diagnosis for defining groups of patients, as PR3-ANCA and MPO-ANCA are associated with different genetic backgrounds, epigenetic expression of autoantigens (PR3 and MPO), epidemiology, clinical features, histopathological findings, and pathogenesis. Furthermore, ANCA specificity affects the phenotype of clinical disease, the patient's initial response to remission-inducing therapy, relapse risk and long-term prognosis. It was found that ANCA serotype (PR3-ANCA positive, MPO-ANCA positive, or ANCA negative) is of equivalent or even higher value than the clinical phenotype (GPA, MPA and EGPA). Taken together, the reclassification of AAV syndromes by ANCA specificity rather than by clinical diagnosis will provides practical diagnosis criteria better aligned by phenotypes, outcomes and treatment responses.

AUTO1-0682
ANCA AND VASCULITIS

LARGE-VESSEL INVOLVEMENT AND AORTIC DILATION IN GIANT-CELL ARTERITIS: A MULTICENTER STUDY OF 549 PATIENTS

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Background

Large-vessel involvement (LVI) can occur in giant-cell arteritis (GCA) and may represent a distinct disease subgroup with a higher risk for aortic dilation. This study aimed to better characterize the presentation and evolution of LVI in patients with GCA.

Method

A retrospective multicenter study enrolled 248 GCA patients with LVI and 301 GCA patients without LVI on imaging. Factors associated with aortic dilation were identified in a multivariable model.

Results

The patients with LVI were younger ($p<0.0001$), more likely to be women ($p=0.01$), and showed fewer cephalic symptoms ($p<0.0001$) and polymyalgia rheumatica ($p=0.001$) but more extracranial vascular symptoms ($p=0.05$) than the patients without LVI. Glucocorticoids (GC) management did not differ between the two groups, but the GC discontinuation rate was lower in the patients with LVI ($p=0.0003$). Repeated aortic imaging procedures were performed at 19 months [range: 5-162 months] and 17 months [range: 6-168 months] after diagnosis in 154 patients with LVI and 123 patients without LVI, respectively, of whom 21% and 7%, respectively, presented new aortic dilations ($p=0.0008$). In the patients with LVI, aortic dilation occurred on an aorta segment shown to be inflammatory on previous imaging in 94% of patients. In the multivariate analysis, LVI was the strongest predictor of aortic dilation (hazard ratio: 3.16 [range: 1.34-7.48], $p=0.009$).

Conclusion

LVI represents a distinct disease pattern of GCA with an increased risk of aortic dilation. Control of the aortic morphology during follow-up is required.

AUTO1-0122
ANCA AND VASCULITIS

TOCILIZUMAB AND REFRACTORY TAKAYASU DISEASE: FOUR CASES REPORTS AND SYSTEMATIC REVIEW

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Background

Relapses upon corticosteroids tapering and immunosuppressive agents are frequent in Takayasu arteritis (TA). Interleukin- 6 is highly involved in physiopathology of TA. Many reports showed efficacy of tocilizumab (TCZ) in refractory TA cases. We report four cases and an updated literature review on the TCZ efficacy and safety in patients with TA.

Method

Patients with TA defined by ACR 1990 criteria were included. Clinical, biological and imaging data were retrospectively reported. Disease activity was analyzed before TCZ and during the follow-up. Medline database was searched for systematic literature review.

Results

One hundred and five patients (median age 28 years [22-38]) were included, mostly refractory cases (76 patients, 72 %). Median TCZ duration was 12 months [6-20]. Among 105 patients, 90 patients (85.7 %) had an initial clinical response within three months [3-6] and 43/66 patients (65.2 %) had a radiological improvement. Only seven patients (9 %) showed relapse on therapy. Corticosteroid dose reduction was obtained in 75/83 patients (90.4 %). Relapse after TCZ discontinuation was observed in six patients (46 %), with a median time of five months [2-9]. Twenty- four side-effects were noted in 18 patients (18 %), with TCZ interruption in seven cases (7 %): 10 infections, five cytopenia, six hepatitis, one pancreatitis, one cutaneous rash and one breast cancer.

Conclusion

This review confirms that TCZ is safe and effective in refractory cases of TA and TCZ is a corticosteroid-sparing therapy in patients with or without previous TNFα blockers therapy. However relapses after TCZ discontinuation are frequent.

AUTO1-0226
ANCA AND VASCULITIS

MPO-ANCA TRIGGER OXIDATIVE BURST, LEADING TO RENAL VASCULITIS IN MICROSCOPIC POLYANGIITIS

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Background

Pauci-immune glomerulonephritis is a serious complication of microscopic polyangiitis (MPA), a disease belonging to the group of ANCA-associated small-vessel vasculitides. In MPA, we previously demonstrated the pathogenic role of anti-myeloperoxidase (MPO) antibodies (ANCA) that trigger oxidative stress through MPO activation and HOCl production, leading to endothelial injury and lung fibrosis. Herein, we investigated the role of MPO-driven oxidative stress and anti-oxidant defences in the development of renal vasculitis in these patients.

Method

Through a prospective cohort of MPA glomerulonephritis, we analysed histological data and determined serum-mediated HOCl production, advanced oxidation protein products (AOPP), and thiol concentration.

Results

Among 38 MPA patients enrolled, renal histological lesions of glomerulonephritis were classified as focal in 50%, crescentic in 15.8%, and mixed in 34.2% of cases. MPA sera triggered higher HOCl production under MPO activation ($p<0.001$), displayed higher AOPP ($p<0.001$) and thiol ($p<0.01$) levels, in comparison with healthy subjects. Higher serum-mediated HOCl production and lower thiol levels ($p=0.022$) at disease onset were associated with the presence of cellular crescents ($p=0.049$). Conversely, higher thiol levels were associated with focal lesions ($p=0.042$), and less interstitial fibrosis ($p=0.039$). HOCl production was decreased during remission ($p<0.01$), whereas thiol concentration remained high ($p=0.39$).

Conclusion

These results suggest that oxidative burst resulting from MPO activation by ANCA contribute to the establishment of glomerulonephritis, a process counterbalanced by anti-oxidant defences such as thiols, which may protect against the development of glomerulosclerosis in renal vasculitis.

AUTO1-0738
ANCA AND VASCULITIS

AORTITIS IN GIANT CELL ARTERITIS: DIAGNOSIS WITH FDG PET/CT AND AGREEMENT WITH CT ANGIOGRAPHY

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Background

To assess the detection rate of aortitis in Giant Cell Arteritis (GCA) with Fluorodeoxyglucose Positron Emission Tomography (PET) and to compare the findings with CT Angiography (CTA).

Method

Fifty-two GCA patients and 27 controls were included. GCA patients had a PET at diagnosis (35/52) or during relapse (17/52). Concomitant CTA was performed in 35/52. Aortitis definition was: FDG uptake>liver for PET and wall thickness ≥ 3mm for CTA. Agreement between PET and CTA was evaluated by Kappa coefficient and Spearman correlation.

Results

Aortitis was diagnosed with PET in 40% (14/35) at diagnosis, and in 0/27 controls. Agreement was perfect between PET and CT (kappa: 0.72 to 1). PET was positive in 35% (6/17) in relapsing GCA: aortitis (n=4) and/or articular uptake (n=4). Discrepancies between PET and CT were observed only in relapsing GCA (n=3). Correlations between Maximum Standardized Uptake Value and wall thickness was moderate at diagnosis (r: 0.57 to 0.7), and not significant during relapse.

Conclusion

Detection rate of aortitis in GCA with PET is 40% using visual analysis, figure in the range of CTA rates, suggesting that the two techniques have similar sensitivity. PET seems interesting in relapsing GCA, letting for detection of vascular and articular activity.

AUTO1-0198
ANCA AND VASCULITIS

CHILDHOOD- VS. ADULT-ONSET ANCA-ASSOCIATED VASCULITIDES: A NESTED, MATCHED CASE–CONTROL STUDY FROM THE FRENCH VASCULITIS STUDY GROUP REGISTRY

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Background

Whether ANCA-associated vasculitides (AAVs) in children (cAAVs) differ from adult-onset AAVs (aAAVs) is still not known.

Method

Demographic and clinical data and disease outcomes of consecutive patients (age <18 years at diagnosis) with cAAVs were compared to a randomly selected sample of aAAV patients from the French Vasculitis Study Group (FVSG) registry. Cases and controls were matched for the following features: AAV (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA] or eosinophilic granulomatosis with polyangiitis [EGPA]), sex, year of enrollment. Prospectively collected information included medications, and disease activity and damage as assessed by the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index, respectively. Relapses, survival rates and causes of death were analyzed.

Results

Thirty-five cAAV cases (25 GPA, 4 MPA, 6 EGPA) were compared with 151 aAAV controls (106 GPA, 17 MPA, 28 EGPA). Respective median ages (range) were 14 (2–17) vs. 53 (18–87) years, with median AAV follow-up durations of 71 and 64 months (P=0.49), respectively. At study entry, children had less frequent myalgias (P=0.005) and peripheral neuropathy (P<0.001) but were more frequently febrile (P<0.05). Their first remission-induction regimens were comparable (P=0.13), most frequently combining glucocorticoids and an immunosuppressant. During follow-up, cAAV patients had a higher overall relapse rate (P<0.05) and, at last visit, had accumulated more damage, mostly ENT sequelae (P=0.001), associated with longer maintenance therapy (P=0.03) than for aAAV controls. Four cAAV and 13 aAAV patients died (P=0.54).

Conclusion

cAAVs are severe diseases, characterized by a higher relapse rate, more accrued damage, and longer maintenance therapy than aAAVs.

AUTO1-0532
ANCA AND VASCULITIS

ANTI-EOSINOPHIL AUTOANTIBODIES DETECTED DURING ANCA SCREENING

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Background

Anti-neutrophil cytoplasmic autoantibodies (ANCA) are commonly found in vasculitis. However, the existence and clinical relevance of anti-eosinophilic auto-antibodies (AEOSA) remains still unclear. AEOSA have been closely associated with primary biliary cholangitis and more loosely associated with other auto-immune conditions affecting the liver, kidneys and joints.

Method

In the Gothenburg region in Sweden, approximately 20-30 patients yearly display AEOSA. The goal of the current study is to determine if the detection and the antigenic specificity of AEOSA are of clinical use.

Results

In the Department for Clinical Immunology, around 1% of the sera tested for the presence of ANCA by immunofluorescence (IF) were positive for AEOSA. Patients positive for AEOSA were included during 2014-2017 (n=35). AEOSA were seen in combination with ANCA (15/35, 43%) or in the absence of ANCA (20/35, 57%). Eosinophil Peroxidase (EPX) was detected as the main autoantigen in 66% of sera. AEOSA+/ANCA+ sera reacted with EPX in 72% of cases, while AEOSA+/ANCA- sera reacted with EPX in 63% of cases. On average, the AEOSA+/ANCA+ patients were 3.5 years older than the AEOSA+/ANCA- group. Women were overrepresented in both groups: 65% in the AEOSA+/ANCA- and 74% in the AEOSA+/ANCA+ group. Eosinophil Cationic Protein (ECP) was also identified as target of AEOSA. The presence of AEOSA was associated with various clinical symptoms where liver, kidney, auto-immune thyroid disease and involvement of gastrointestinal tract were overrepresented.

Conclusion

We confirm that EPX is a target of auto-antibodies. The significance and the pathogenic potential of AEOSA is still under investigation.

AUTO1-0330
ANCA AND VASCULITIS

PERICARDITIS AMONG GCA PATIENTS: FROM MYTH TO REALITY

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Background

Giant cell arteritis (GCA) is an inflammatory disease of unknown etiology which affects adults over the age of 50. GCA (also known as temporal arteritis) is a vasculitis of large and medium-sized vessels which involves the extracranial branches of the carotid artery. Common manifestations include constitutional symptoms, headache, jaw claudication, scalp tenderness and vision loss. Cardiac involvement in GCA is considered to be as low as 5%, and less than 30 cases of pericarditis among GCA patients have been reported in the literature. The aim of this study was to evaluate the association between GCA and pericarditis by conducting a cross-sectional study utilizing the database of the largest healthcare provider in Israel.

Method

The proportion of past documentation of pericarditis amongst patients diagnosed with GCA was compared with that of their age- and gender-matched controls. Univariate analysis was performed using Chi-square and t-test; multivariate analysis was performed using logistic regression.

Results

The study included 5,659 GCA patients and 28,261 controls. GCA patients had higher rates of cardiovascular risk factors. Pericarditis was observed in 69 GCA patients and 96 controls (1.22% vs. 0.34%, respectively, $p<0.001$), significantly higher among GCA patients in comparison with controls. A significant interaction was found between GCA, pericarditis and young age (<70 years).

Conclusion

The study showed an independent association between GCA and pericarditis, especially among young patients. Proper screening should be applied whenever a suspicion arises as to the existence of comorbidity in patients with either disease.

AUTO1-0710
ANCA AND VASCULITIS

AUTOANTIGENSPECIFIC TH22 AND TH17 CELLS INFLAME THE KIDNEY IN ANCA-VASCULITIS AND MEDIATE RENAL DAMAGE

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Background

Anti-neutrophil-cytoplasmic-antibody (ANCA)-associated-vasculitis (AAV) is an autoimmune small-vessel-vasculitis. T-cells play a pivotal role in pathogenesis as drivers of autoantibody formation and vasculitic damage. However, the involvement of T-cells in renal vasculitis is understood poorly. It is the aim to this study to investigate the dynamics of renal T-cell inflammation in a rat model of AAV.

Method

Wistar-Kyoto-rats were immunized with myeloperoxidase (MPO) in Freunds Adjuvant to induce AAV. Control rats were immunized with Freunds Adjuvant only. Albuminuria was determined weekly and rats were culled after two, four and six weeks. At the time of harvest, renal T-cells were isolated and characterized by flow cytometry. Antigen-specificity was determined by ELiSPOT. Gene expression was determined by PCR.

Results

MPO-rats developed detectable titres of anti-MPO by week two. By week six, all MPO-animals (n=20) but one developed significant albuminuria. Accordingly, MPO animals showed significant crescent formation as compared to the controls (% of affected glomeruli: 11.4 ±10.5% vs. 0.4 ±0.7%, $p<0.005$). From week two on, Th17 and Th22 cells inflamed the kidney as determined by PCR and/or flow cytometry in MPO-rats. The Th17 and Th22 infiltrate was heaviest at week six post-immunization. The intra-renal T-cell response was skewed towards Th17 as compared to the frequency of splenic Th17 cells in MPO-rats (9.1 ±4.3% vs. 1.9 ±0.6%, $p<0.005$). The majority of intra-renal Th17 and Th22 cells was MPO-specific. Control rats did not shown renal T-cell infiltration.

Conclusion

Th17 and Th22 cells are drivers of renal inflammation in ANCA-vasculitis. IL-17 blockade may have a therapeutic role in renal AAV.

AUTO1-0149
ANCA AND VASCULITIS

RITUXIMAB INDUCTION WITHOUT MAINTENANCE FOR PR3-ANCA ASSOCIATED VASCULITIS END STAGE RENAL DISEASE AND DIALYSIS

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Background

ANCA associated vasculitis may lead to irreversible organ damage particularly end-stage renal disease requiring dialysis. Only 5% of GPA patients with end-stage kidney disease will eventually wean off dialysis.

Method

We present a 32 year old female admitted for pulmonary nodules, nephrotic syndrome with acute renal failure and elevated PR-3 ANCA.

Results

The renal biopsy histopathology revealed pauci-immune crescentic glomerulonephritis small-vessel vasculitis leading to the diagnosis of granulomatosis polyangiitis (GPA). The patient received IV pulse steroids followed by high dose oral prednisone. Immunosuppressive induction therapy with IV Rituximab (375 mg/m²) was administered weekly for 4 weeks. Rapid deterioration of her kidney failure led to massive volume overload and pulmonary edema requiring intensive care (ICU) hospitalization. In the ICU, hemodialysis and plasmapheresis were initiated. Improvement slowly ensued, however the patient remained dialysis dependent. She was discharged on high-dose prednisone which was gradually tapered. On follow-up, the patient continued to improve and became dialysis free 8 months later. No additional immunosuppressive maintenance therapy with Rituximab was administered due to the recent data suggesting no added benefit after Rituximab induction therapy in certain patients. Moreover, in patients on chronic dialysis, excessive immunosuppression may be detrimental. Despite the prolonged dialysis dependence, the patient regained renal function and was dialysis free with maintenance treatment of oral corticosteroids. To date, the patient has been in complete remission for 26 months and without vasculitis flares.

Conclusion

We suggest that rituximab induction without maintenance for PR3-ANCA associated vasculitis end stage renal disease and dialysis may be sufficient.

AUTO1-0365
ANTIPHOSPHOLIPID SYNDROME

ARTERIAL STENOSIS IN ANTI-PHOSPHOLIPIDS SYNDROME: A LITTLE-KNOWN ENDOTHELIAL DISEASE.

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Background

First described in 1983, antiphospholipid syndrome (APS) is an autoimmune condition characterized by the occurrence of recurrent arterial and/or venous thrombosis, and/or pregnancy morbidity, in the setting of persistent presence of antiphospholipid antibodies (aPL).While thrombosis is the most well-known pathogenic mechanism in this disorder, the relevance of some other mechanisms such as arterial stenosis is being increasingly recognized.

Method

We performed a review based on a clearly formulated question and we identified the most relevant studies related to this topic.

Results

Arterial stenosis has been first described in the renal arteries in patients with APS. However, intracranial and coeliac arteries can also be involved with treatable clinical manifestations. The pathophysiology of this stenotic arterial vasculopathy is not fully understood but some recent studies revealed new insights into the molecular mechanisms behind this endothelial cell activation in APS. Indeed, endothelial cell activation seems to be a central mechanism in the pathogenesis of APS. Pathogenic aPL have been shown to have direct effects on endothelial cells, both in vivo and in vitro, leading to adhesion molecule upregulation and pro-inflammatory cytokine secretion. Furthermore, recent studies suggested that the activation of mTORC (mammalian target of rapamycin complex) stimulates intimal hyperplasia, leading to the chronic vascular lesions associated with APS. In this review, we discuss also the clinical manifestations and the different imaging modalities used for the diagnosis.

Conclusion

It is very important to recognize arterial stenosis in APS patients, as it may be a treatable cause for hypertension, renal, CNS and gastrointestinal manifestations of the disease.

AUTO1-0697
ANTIPHOSPHOLIPID SYNDROME

A LARGE CASE SERIES OF PATIENTS TESTED POSITIVE FOR ANTIPHOSPHOLIPID ANTIBODIES IN THE NETHERLANDS – A CLINICAL DESCRIPTION

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Background

Antiphospholipid syndrome (APS) is a rare autoimmune disease characterized by venous and/or arterial thrombotic events or pregnancy morbidity, and the presence of plasma antiphospholipid antibodies (aPL). Data on burden of disease of APS are lacking in the Netherlands. We identified all aPL-positive patients in our hospital over the past ten years, and determined the proportion of APS and APS related events.

Method

This study was conducted in the University Medical Center Utrecht, the Netherlands. Over the past ten years, all patients with positive aPL testing were identified through the laboratory data management system. All medical files were reviewed; data on diagnosis (primary APS, systemic lupus erythematodes, obstetric APS (oAPS)) and thrombotic complications were registered.

Results

Characteristic	Total (N = 483)
Female seks – no (%)	389 (80.5)
Age – median, yr (IQR)	48 (39-58)
Mortality – no (%)	7 (1.5)
Primary antiphospholipid syndrome – no (%)	68 (14.1)
Secondary antiphospholipid syndrome – no (%)	95 (19.7)
Obstetric antiphospholipid syndrome – no (%)	53 (10.1)
aPL positive, no antiphospholipid syndrome – no (%)	255 (52.8)

483 Patients were identified (median age 48 yrs (IQR 39-58); female sex 389 (80.5 %); 192 patients (39.8%) APS). *Table 1: patient characteristics*

7 Patients died during the studied period. 68 Patients had primary APS and 95 patients secondary APS; a total of 124 deep venous thromboses, 77 pulmonary embolisms, 30 arterial thromboses and 95 cerebrovascular accidents (CVA) were observed. 7 Patients had catastrophic antiphospholipid syndrome. Triple positive patients did not have higher chances of venous thrombosis than other APS patients; however, chances of CVA were significantly higher (p = 0.001).

Conclusion

Almost half of the patients tested for aPL were diagnosed with APS. Patients with a high risk triple positive aPL-profile did not have higher chances to develop venous complications; however, a higher incidence of arterial events was found in this group.

AUTO1-0749
ANTIPHOSPHOLIPID SYNDROME

ANGIOGENIC FACTORS IN PREGNANCIES WITH ANTIPHOSPHOLIPID SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

An imbalance of angiogenic placental factors such as endoglin, soluble fms-like tyrosine kinase 1(sFlt-1) and placental growth factor (PlGF) has been implicated in the pathophysiology of preeclampsia. The aim of the present study was the evaluation of serum levels of sFlt-1, PlGF and endoglin in women with primary and secondary APS and SLE longitudinally during pregnancy for early detection of preeclampsia.

Method

Serum levels of sFlt-1, PlGF and endoglin were measured prospectively at 4-week intervals (from gestational weeks 12 to 36) in 17 women with primary APS (PAPS), 18 women with secondary APS (SAPS), and 23 women with SLE.

ResultsWomen with APS and SLE who developed preeclampsia had significant higher median sFlt-1 and endoglin levels and a significant higher sFlt-1/PlGF ratio, as well as significant lower median PlGF-levels compared to women with APS and SLE and without preeclampsia starting from 12 weeks of gestation on. These differences increased with gestational age . The sFflt-1/PlGF ratio became a significant predictor for preeclampsia at 12 weeks, showing the highest levels at 20, 24 and 28 weeks of gestation.**Conclusion**

Angiogenic factors can predict preeclampsia in women with APS and SLE in early pregnancy. The sFflt-1/PlGF ratio became a significant predictor for preeclampsia in early gestation at 12 weeks, with the highest levels at 20, 24 and 28 weeks. .

Endoglin, sFlt-1 and PlGF are potential screening parameters for the development of preeclampsia in pregnant women with autoimmune diseases.

AUTO1-0540
ANTIPHOSPHOLIPID SYNDROME

ANTIBODIES AGAINST S100A10 PROTEIN IN ANTIPHOSPHOLIPID SYNDROME

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Background

Annexin A2 (ANXA2), an endothelial cell receptor for plasminogen and tissue plasminogen activator, has been identified as a new autoantigen in antiphospholipid syndrome (APS). ANXA2 can exist as a monomer or a heterotetrameric complex with S100A10 protein.
This S100A10 subunit plays also a pivotal role in the regulation of fibrinolysis. The aim of this study was to evaluate the prevalence of autoantibodies directed against S100A10 protein in patients with APS.

Method

Patients with primary APS (PAPS) and patients with systemic lupus erythematosus (SLE) were included retrospectively in this study. Anti-S100A10 IgG and IgM antibodies were detected, using an ELISA, in the serum of patients. The cut-off value for positivity was defined as 3 standard deviations above the mean optical density (OD) obtained in the sera from 100 healthy individuals.

Results

The study group consisted of 100 healthy individuals and 86 patients : 44 APS patients (26 PAPS patients and 18 SLE patients with APS) and 42 SLE patients without APS. The median age of APS patients, SLE patients without APS and healthy individuals was 45, 38.5 and 42 years, respectively. The prevalence of anti-S100A10 antibodies was 11.3%, 2.3% and 2% in APS patients, SLE patients without APS and healthy individuals respectively. High levels of anti-S100A10 were observed in sera from one PAPS patient and two SLE patients with APS.

Conclusion

We identified S100A10 protein as a target of autoantibodies in sera from patients with APS. Further studies are required to determine whether these antibodies could play a role in thrombogenic mechanisms of APS.

AUTO1-0218
ANTIPHOSPHOLIPID SYNDROME

EVALUATION OF A NOVEL LINE IMMUNODOT ASSAY FOR ANTIPHOSPHOLIPID ANTIBODIES REVEALS SUPERIOR DIAGNOSTIC PERFORMANCES FOR ANTIBODIES AGAINST ANIONIC PHOSPHOLIPIDS

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Background

Antiphospholipid antibodies (aPL) constitute the laboratory hallmark of the antiphospholipid syndrome (APS). aPL are commonly investigated with ELISA systems. New assay formats suited to multiplexing are, however, emerging. We evaluated the diagnostic performance of a novel line immunodot assay enabling the simultaneous detection of 10 different aPL.

Method

53 APS patients and 34 healthy controls were included. Sera were investigated for the criteria aPL anti-cardiolipin (aCL) and -β2-glycoprotein I (aβ2-GPI) and the non-criteria aPL anti-phosphatidic acid (aPA), -phosphatidyl-choline (aPC), -ethanolamin (aPE), -glycerol (aPG), -inositol (aPI), -serine (aPS), -annexin V (aAnnV) and -prothrombin (aPT) with the *anti-phospholipid 10 dot* from Generic Assays (GA). Criteria aPL were as well determined with the Alegria (ALE), Acustar (ACU), Unicap (UNI), and Aeskulisa (AES). Non-criteria aPL were additionally measured with the AES system. Diagnostic performance of the immunodot for criteria aPL was assessed employing a “consensus” gold standard calculated via latent class analysis. Results for non-criteria aPL were evaluated with the clinical diagnosis as gold standard.

Results

For criteria aPL, the immunodot exhibits sensitivities and specificities comparable to the ALE, ACU, UNI, and AES. For non-criteria aPL, sensitivies of the immunodot for aPA-, aPI-, aPS-IgG and aPA-IgM were significantly better and for aPC-, aPE-, aAnnV-IgG and aPC- and aPE-IgM significantly worse than AES. Specificities did not differ significantly.

Conclusion

The immunodot performs equally well as established immunoassays for criteria aPL. With respect to non-criteria aPL, the immunodot offers advantages in the detection of antibodies against anionic phospholipids. In contrast, aPL against neutral phospholipids were determined less frequently.

AUTO1-0026
AUTOIMMUNE AUTONOMIC NERVE DISEASES AND CHANNELOPATHIES: IMMUNOTHERAPY WITH IVIG AND BEYOND

INTRAVENOUS IMMUNOGLOBULIN (IVIG) IN THE VANGUARD THERAPY OF SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis (SSc) is a rare autoimmune disease that is characterized by a progressive skin fibrosis, an obliteration of the microvasculature and an exaggerated extracellular matrix deposition. Those phatophysiolofgical alterations result in a multi systemic dysfunction and the symptoms depend on the affliction of each organ.

The therapy for SSc ranges between corticosteroids to hematopoietic stem cells transplantation, depending on the tissue affected. Until today, none of the therapies have been described as a successful anti-fibrotic therapy and almost have demonstrated a limited efficacy. There are different reasons that can justified this unsuccessful response beyond SSc therapy: the underlying pathogenic mechanism of the disease is still undefined; most of the interventional therapies are based on case series; in the cohort studies, patients during different phases of the disease were recruited.

Method

We reviewed the latest articles about IVIG therapy in patients with systemic sclerosis, after a research on Pubmed database. We analyzed the results presented in each, presenting the evidence of this therapy.

Results

The rational use of IVIG in SSc has a pathological background and recent studies show IVIG as an efficacious and safe therapy in SSc. Its success is so far described on muscle, skin and joint involvement as well in corticosteroid tapering. The lung disease is still a challenge, but more studies are required.

Conclusion

IVIG has demonstrated a great option therapy in patients with systemic sclerosis and we recommend the inclusion of IVIG in the guidelines of this harmful disease.

AUTO1-0614
AUTOIMMUNE AUTONOMIC NERVE DISEASES AND CHANNELOPATHIES: IMMUNOTHERAPY WITH IVIG AND BEYOND

A PILOT STUDY OF IVIG FOR AUTISM;IMPACT ON AUTISM SPECTRUM AND NEUROINFLAMMATION

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Background

Research has shown that a subset of the ASD population presents with immune dysregulation. To explore this topic further, we investigated the efficacy and tolerability of intravenous immunoglobulin (IVIG) infusion in children with ASD. Participants were recruited based on a diagnosis of autistic disorder.

Method

15 completed the trial and received IVIG treatment (1 g/kg dose) for ten 21-day treatment cycles. The primary endpoint was disease improvement assessed using standardized cognitive and behavioral tests (Children's Communication Checklist [CCC-2], Social Responsiveness Scale [SRS], Aberrant Behavior Checklist [ABC], Clinical Global Impressions-Severity [CGI-S] and -Improvement [CGI-I], Autism Diagnostic Observation Schedule [ADOS], and Peabody Picture Vocabulary Test [PPVT]). Secondary endpoints included experimental biomarkers such as CD154, toll-like receptor-4, memory B cells, FOXP3, and lymphocyte stimulation

Results

Significant improvements from baseline to study endpoint were observed in several subscales of the CCC-2, SRS, CGI-I, CGI-S, and ADOS, including Associated Maladaptive Behaviors ($p \leq .043$), Reciprocal Social Interaction ($p = .015$), Communication ($p < .001$), and Stereotyped Behaviors and Repetitive Interests ($p \leq .013$). Statistically significant reductions were also seen in numerous secondary outcomes of immunological biomarkers indicative of neuroinflammation. IVIG was well tolerated; no subjects withdrew due to an adverse event, and clinical data showed no evidence of thromboembolic events.

Conclusion

These data suggest that epigenetic triggers may interact with a dysfunctional immune system in some patients with autism, and IVIG treatment may exert a positive impact on behaviors and markers of inflammation in ASD. Nevertheless, further evaluation in studies with larger populations is warranted.

AUTO1-0002
AUTOIMMUNE AUTONOMIC NERVE DISEASES AND CHANNELOPATHIES: IMMUNOTHERAPY WITH IVIG AND BEYOND

FUNCTIONAL AUTOANTIBODIES AND FUNCTIONAL AUTOANTIBODY DISEASE – A GLANCE AT THE PAST, PRESENCE AND FUTURE.

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Autoimmunity is increasingly accepted as the origin or amplifier of various diseases. While classic autoantibodies (AABs) induce immune responses resulting in destruction of the affected tissue, an additional class of AABs is directed against G-protein-coupled receptors (GPCRs; GPCR-AABs). GPCR-AABs functionally affect their related receptors but mechanisms to prevent over-boarding effects that are known for physiologic receptor ligands are lacking. GPCR-AAB-associated diseases with evidence for disease-specific pathogenicity could be named “functional autoantibody disease”. The story of GPCR-AABs started in 1974 with the publication of “Chagasic cardiopathy. Demonstration of a serum gamma globulin factor which reacts with endocardium and vascular structures”. Thereafter, the GPCR-AABs’ causative or at least supportive role in cardiovascular diseases were the center of interest for many years. However, the pathogenicity of GPCR-AABs is not restricted to cardiovascular diseases or diseases closely related to these. GPCR-AABs are currently receiving increasing attention, e.g. in diseases at first glance far from the cardiovascular system, such as dementia, Alzheimer’s disease, complex regional pain syndrome (CRPS), fatigue syndrome and even including human papilloma virus (HPV) vaccination. Consequently, the establishment and continuous development of treatment strategies to counteract GPCR-AABs should have priority for the future. In this context, two different treatment lines could be promising: first, the elimination of GPCR-AABs from the patients’ circulation by plasmapheresis or immunoadsorption, and second, the patients’ in vivo treatment for GPCR-AAB attack by IVIG treatment, B-cell depletion or in vivo binding and neutralization of the GPCR-AABs.

AUTO1-0046
AUTOIMMUNE AUTONOMIC NERVE DISEASES AND CHANNELOPATHIES: IMMUNOTHERAPY WITH IVIG AND BEYOND

CLINICAL INDICATIONS FOR INTRAVENOUS IMMUNOGLOBULIN (IVIG) UTILIZATION IN A TERTIARY MEDICAL CENTER: A 9-YEAR RETROSPECTIVE STUDY

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Background

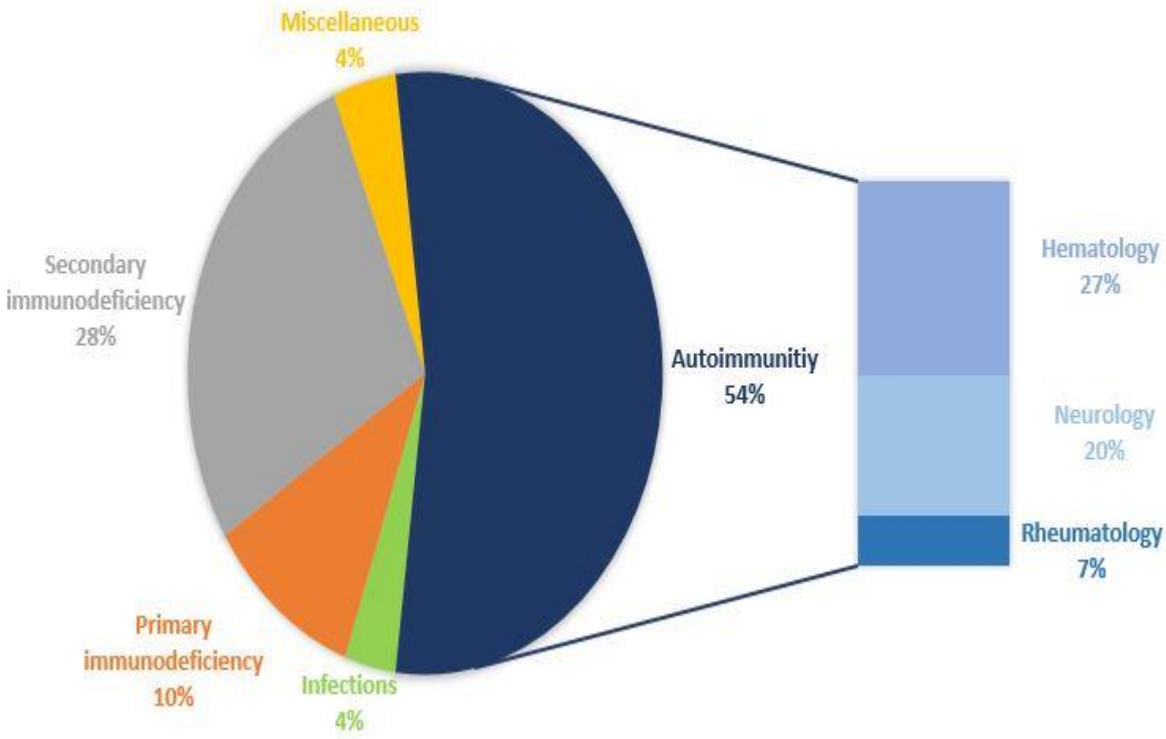
Intravenous immunoglobulins (IVIG) are a biological product originally developed to treat immunocompromised patients. In the last decades, there has been increased utilization of IVIG in autoimmune conditions.
Our objectives are to evaluate the clinical use of IVIG in the largest tertiary medical center in Israel, determine top uses and estimate off-label usage and assess consumption of this blood product.

Method

We conducted an observational, retrospective study involving all patients who received IVIG from 2007 through 2015. Subjects were classified into five groups according to the indication for treatment.

Results

A total of 1,117 patients were identified. The mean (±SD) age of adults and children were 55±17 and 8±7 years, respectively. Most common indication for treatment were immune-mediated conditions (54%), followed by secondary immunodeficiency (28%), primary immunodeficiency (10%), infections (4%) and miscellaneous (4%). The main Immune-mediated conditions treated were hematological disorders (305 patients, 27%), neurological disorders (219 pts, 20%) and rheumatologic conditions (79 pts, 7%). Overall, A statistically significant change in study period was observed in the number of patients ($p<0.001$), consumption of IVIG ($p<0.01$) and amount of IVIG administered per patient ($p<0.01$). Fifty six percent of the IVIG infusions were given for off-label FDA (Food and Drug Administration) indications.



Conclusion

In this study, we demonstrated that immune-mediated conditions represent the majority of indications for treatment with IVIG. We observed a 417% increase in IVIG administration

AUTO1-0037
AUTOIMMUNE AUTONOMIC NERVE DISEASES AND CHANNELOPATHIES: IMMUNOTHERAPY WITH IVIG AND BEYOND

ALZHEIMER'S DISEASE, AUTOIMMUNITY AND INFLAMMATION

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Background

Alzheimer's disease (AD) is the most common cause of dementia involving 13 million people worldwide with an economic burden of 605 billion Dollars. The neuropathology presents: Extra-cellular Beta amyloid (Aβ) Senile plaques; the tau protein (NFT) within the neurons; vascular damage; microglia and synaptic pathology. Inflammation and the immune system's contributes to disease onset and progression.
Pros for an autoimmune mechanism are: female preponderance, presence of autoantibodies in the brain of AD patients and the close association with Hashimoto thyroiditis.
Three stages of **cognitive decline** can be defined: 1. Preclinical; 2. Mild cognitive impairment (MCI); 3. Overt Dementia.
Immunotherapy of AD aim at attenuation of innate inflammatory response and at modulation of the adaptive immunity and Aβ clearance.

Method

The current literature was reviewed.

Results

Innate immune system involvement, represented by: 1. The complement system which mediates inflammation, clears damaged cells and Aβ oligomers and facilitates neuronal death. 2. Activated chemokine system. 3. Over expression of toll like receptor.
The involvement of the **adaptive immune system** is manifested by: 1. A lower number of naïve T lymphocytes. 2. Early elevated soluble plasma CD40/CD40L. 3. increased number of activated CTL's and Helper T cells.

All these phenomena are negatively correlated with cognitive test results.

Reviewed will be:
-NSAIDS trials in mice and patients.
-Active immunization with different Aβ vaccines.
-Passive immunization, with monoclonal antibodies.
-Intravenous high dose IgG.
-AD-specific IVIG.

Conclusion

Late intervention is expected to have limited benefit, whereas an early one, is expected to elicit clinical improvement and possibly avoid dementia.

AUTO1-0791
AUTOIMMUNE BLOOD DISEASES AND ATHEROSCLEROSIS

ALPHA-DEFENSINS LINK INNATE IMMUNITY, ATHEROSCLEROSIS AND THROMBOSIS

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Heparin-induced thrombocytopenia (HIT) is a potentially devastating autoantibody-mediated thrombotic disorder that develops in ~1% of patients treated with unfractionated heparin. HIT is caused by antibodies (Abs) to complexes that form between a polyanionic hapten (e.g. heparin (H) or glycosaminoglycans (GAGs)) and platelet factor 4 (PF4), the predominant protein secreted by activated platelets. The resultant ultralarge immune complexes, which exceed 1 μm in size, activate Fcγ receptors on platelets, monocytes and neutrophils and activate endothelial cells to generate thrombin, which back amplifies intensely prothrombotic pathways. Treatment with maximally tolerated doses of thrombin or factor Xa inhibitors reduces new thromboembolic events but without reducing mortality or amputations (~10% each) and at a risk of major bleeding estimated to be ~1%/day for which there is no antidote.

Over 50% of all patients develop anti-PF4/H Abs after receiving unfractionated heparin for cardiac bypass surgery, an incidence that is >10-fold above the incidence of clinical HIT. This raises questions as to: 1) how a constituent host protein (PF4) is converted to an autoantigen by H in the presence of a constituent hapten such as GAGs in otherwise immunologically normal hosts, and 2) how only a subset of these antibodies are pathogenic. To address these questions, the PENN/Duke team first recapitulated the salient features of HIT (thrombocytopenia and thrombosis) in a passive immune model in mice genetically depleted of endogenous PF4 that express human PF4 and human FcRγIIA receptors followed by injection of a mouse anti-PF4/heparin monoclonal Ab (KKO) that competes with human anti-PF4/H Abs from patients with HIT, but not those found in asymptomatic antibody positive individuals.

In conjunction with the Greene group, we then studied the structure of the immune complex itself. PF4 is an asymmetric tetramer that is in equilibrium with monomers and dimers. Tetramers oligomerize in the presence of heparin and “superoligomerize” when exposed to KKO or human HIT Abs. We then described the co-crystal structures of PF4 complexed with the heparin fragment fondaparinux and with KKO or with an isotype matched monoclonal anti-PF4 Ab RTO. We found: 1) Fondaparinux binds to one side of the asymmetric PF4 tetramer, stabilizing a contralateral epitope that comprises the binding site for KKO; 2. Polyanions such as heparin form stable linear structures that permit PF4 tetramers to assemble and oligomerize; 3. The CDRs of KKO (and likely competing pathogenic human HIT Abs) interface with three of the four monomers in the PF4 tetramer, implying that heparin both increases HIT Ab affinity and promotes oligomerization of tetramer which enhances Ab avidity; 4. The isotype control Ab RTO binds to PF4 monomers at a site that overlaps with KKO; 5. RTO both prevents and disrupts formation of ultralarge complexes between PF4, heparin and KKO in vitro; 6. RTO prevents KKO-induced platelet and fibrin accretion in the mesenteric vessels of HIT-susceptible mice.

These data provide new insights into the mechanism by which an extended highly sulfated polyanion such as unfractionated heparin converts a constituent host protein into a potent autoantigen, how only a subset of anti-PF4/H antibodies become pathogenic, and suggests that disrupting the inciting autoantigen may provide a novel and rationale non-anticoagulant intervention in this autoimmune thrombotic disorder.

AUTO1-0669
AUTOIMMUNE BLOOD DISEASES AND ATHEROSCLEROSIS

ERYTHROCYTE-SPECIFIC ANTIBODY AS A POTENTIAL NEW THERAPEUTIC MODALITY IN AUTOIMMUNE AND INFLAMMATORY DISORDERS

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Background

Anti-D is an effective therapy for patients with immune thrombocytopenia (ITP) but has never been considered in other autoimmune diseases due to its proposed mechanism where it is simply thought to competitively inhibit opsonized platelet clearance by phagocytic cells. A murine erythrocyte-specific antibody (TER-119) is similarly able to ameliorate a murine model of ITP. We have hypothesized TER-119 may have therapeutic potential in other autoimmune diseases.

Method

Inflammatory arthritis was induced by both the K/BxN-serum transfer model as well as the collagen antibody-induced arthritis model and the therapeutic potential of TER-119 evaluated. To examine an unrelated inflammatory disease model, TER-119 was also evaluated for its ability to prevent acute lung injury induced by anti-MHC class I antibody.

Results

TER-119 could prevent the induction of arthritis as well as treat established disease in the K/BxN-serum transfer model. To evaluate the potential mechanism of effect, TER-119 was deglycosylated, which impairs interactions with Fc receptors and complement and this manipulation blocked its therapeutic activity. In the collagen antibody-induced arthritis model, TER-119 dose-dependently reversed established disease activity and associated joint inflammatory cell infiltration. To determine if TER-119 could be effective in inflammatory lung disease, SCID mice were injected with an anti-MHC class I antibody triggering a rapid reduction in body temperature and the development of pulmonary edema. TER-119 offset the drop in body temperature and ameliorated the pulmonary edema.

Conclusion

TER-119 has substantial broad therapeutic activity in antibody-mediated autoimmune and inflammatory disease suggesting that RBC specific antibodies such as anti-D may have significant potential in inflammatory disorders.

AUTO1-0627
AUTOIMMUNE BLOOD DISEASES AND ATHEROSCLEROSIS

AUTOIMMUNE AND ANGIOGENIC BIOMARKERS OF AUTOIMMUNE ATHEROSCLEROSIS

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Background

Cardiovascular disease dependent on inflammatory accelerated atherosclerosis leads to increased mortality in rheumatoid arthritis (RA). In addition to traditional, Framingham risk factors, several immuno-inflammatory cells, mediators and molecules may link atherosclerosis to arthritis.

Method

In this review talk, we will summarize the utility of vascular and angiogenic biomarkers in the assessment of autoimmune atherosclerosis.

Results

Among immune cells, primarily TH1 cells, as well as endothelial cells play a crucial role in synovial and vascular inflammation. Various cell surface molecules, such as adhesion receptors, angiogenic molecules, as well as soluble pro-inflammatory cytokines, chemokines, autoantibodies and proteases have been implicated in RA and vascular damage.

Conclusion

The early assessment of atherosclerosis and early intervention would decrease cardiovascular risk in RA and other autoimmune diseases.

AUTO1-0496
AUTOIMMUNE BLOOD DISEASES AND ATHEROSCLEROSIS

ENDOTHELIAL ACTIVATION IN ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: MECHANISMS AND CORRELATION WITH DISEASE SEVERITY.

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Background

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic micro-angiopathy (TMA) characterized by ischemic events affecting mainly the central nervous system and the myocardium, hemorrhages of various severity, mechanic haemolytic anaemia with schistocytes and deep thrombocytopenia. Acquired form of TTP (a-TTP) is characterized by the presence of anti-ADAMTS13 neutralizing auto-antibodies inducing an accumulation of circulating ultra-large von Willebrand Factor (VWF). ADAMTS13 deficient animals have however also revealed the importance of endothelial cell (EC) activation through UL-VWF release from Weibel-Palade Bodies (WPB) exocytosis.

Method

In this study, we asked whether a-TTP plasma were able to induce rapid EC activation *in vitro*.

Results

We observed that plasma prospectively collected from 24 patients in acute phase a-TTP induced UL-VWF release and WPB exocytosis from ECs in a calcium (Ca^{++})-dependent mechanism and that this effect was correlated with disease severity and prognosis in 60 patients. We then looked for plasma factors present in a-TTP patients able to activate EC. We observed that 1) a-TTP plasma contained high concentrations of free heme and nucleosomes 2) free heme and nucleosomes but not complement, played a minor role in WPB exocytosis and 3) the IgG fraction from a-TTP plasma played a crucial role in Ca^{++}-dependent WBP exocytosis.

Conclusion

Our results confirm that EC activation leading to WPB degranulation and VWF exposure may constitute a central event in TTP pathogenic cascade and demonstrate the multifactorial mechanisms of EC activation.

AUTO1-0301
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

POLY IMPLANT PROTHESE™ (PIP) EXPERIENCE IN FRANCE: LOCAL COMPLICATIONS AND GENERAL MANIFESTATIONS IN 284 PATIENTS

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Background

In March 2010, the French medical regulatory authority withdrew *Poly Implant Prothèse*™ (PIP) breast implants from the market due to the use of non-medical-grade silicone gel by manufacturer. The patients association PPP (*Patientes Porteuses d'implants mammaires* PIP), founded in 2011, carried out a survey of all members to estimate the frequency of general symptoms and local complications of PIP silicone breast implants (SBI). In present study, we analyzed the results of this survey and tried to characterize general symptoms typology and evaluate whether they associated with the presence of SBI dysfunctioning (cracks, rupture) or local complications (LC).

Method

Among the 306 answers collected, 284 were eligible for analysis, including 168 women with general symptoms ('*symptomatic'* group*;* 59%) and 116 without ('*asymptomatic'* group*;* 41%). Subgroups '*aesthetic surgery*' and '*reconstruction*' were defined according to SBI indication.

Results

Most frequent symptoms included fatigue (79.8%), muscle (61.3%) and joint (58.3%) pain, and cognitive complaints (50.6%). 163 (97%) and 136 (81%) symptomatic patients had one or two typical clinical manifestations of ASIA, respectively. SBI dysfunctioning associated with the occurrence of LC and general symptoms (p<0,0001). Dysfunctioning and LC were 3 fold more frequent in *symptomatic* group. The rate of dysfunctioning and LC was comparable between '*aesthetic surgery*' and '*reconstruction*' groups.

Conclusion

This study is suggestive of a relation between SBI dysfunctioning, local complications and the occurrence of general manifestations. This result supports the view that silicone release from BSI could trigger ASIA.

AUTO1-0536
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

ASIA DUE TO IMPLANTED FOREIGN BODIES: WHAT-A-MESH

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Background

Both in hernia repair and in pelvic organ prolapse surgery, polypropylene meshes offer tremendous clinical benefits. Undesirable local effects have been extensively described. Systemic effects, however, are not yet reported. Since biomaterials may induce an immunologic reaction and may act as an adjuvant we postulate that meshes could be a cause of ASIA.

Method

Twenty-five patients referred to my clinic between January 2014 and December 2016 were evaluated for the presence of ASIA.

Results

Twenty consecutive women and five men with a mesh fulfilled the diagnostic criteria for ASIA.
Median age at time of operation was 50 years (range, 28 – 75 years). Twelve patients had a hernia repair and 13 patients had a transvaginal mesh.
All 25 patients presented with fatigue and myalgias or muscle weakness (Table). In 61% of the patients, these symptoms started shortly after the operation whereas in the other patients signs and symptoms developed later on. 72% of patients reported that the mesh caused (severe) pain. 76% of patients had pre-existent allergic disease.
Laboratory examinations revealed (non-specific) abnormalities in all but two patients (Table). Autoantibodies (i.e., antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and/or anti-cardiolipin antibodies) were found in 39% of patients. A diagnosis of well-established autoimmune diseases was made in 56% of patients. In three patients,

the hernia mesh could be removed resulting in (partial) recovery of the disease.

TABLE

Symptoms and Laboratory Findings in 25 patients with a systemic illness after mesh implantation

SYMPTOMS	
Fatigue	100%
Myalgias/muscle weakness	100%
Arthralgias/arthritis	80%
Cognitive impairment	84%
Pyrexia	76%
Dry eyes/dry mouth	80%
Irritable bowel syndrome	80%
Allergy	76%
Painful mesh	72%
LABORATORY ABNORMALITIES	
Elevated CRP	21%
Elevated ACE	25%
Elevated total IgE levels	25%
Elevated CK levels	32%
Decreased IgG levels	14%
Autoantibodies	39%

CRP = C-reactive protein; ACE = angiotensin converting enzyme; IgE = immunoglobulin E; CK = creatine kinase; IgG = immunoglobulin G; Autoantibodies: 4 patients had anti-neutrophil cytoplasmic antibodies; 4 patients had anti-cardiolipin antibodies; 3 patients had anti-nuclear antibodies

Conclusion

Implantation of a polypropylene mesh may result in the occurrence of a systemic disease, i.e., *autoimmunity/auto-inflammatory syndrome induced by adjuvants* (ASIA) especially in patients with a pre-existent allergic disease.

AUTO1-1071
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

SILICONE BREAST IMPLANTS AND DEPRESSION, FIBROMYALGIA AND CHRONIC FATIGUE SYNDROME IN A RHEUMATOLOGY CLINIC POPULATION

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Background: Silicone breast implants (SBI) may induce systemic autoimmune disease as part of an Autoimmune Syndrome Induced by Adjuvants (ASIA). This syndrome bears some similarities to fibromyalgia and chronic fatigue syndrome (CFS). We sought to determine whether there are any associations between SBI and depression, fibromyalgia and CFS in a rheumatology clinic population.
Methods: The electronic files of Rheumatology clinic patients at the Royal Adelaide Hospital between 2000 and 2017 were searched for patients who had received SBI prior to rheumatological diagnosis. Demographics, diagnosis, implant history and whether the patient had depression, fibromyalgia or CFS were recorded. Controls were Rheumatology clinic patients, half of whom had systemic sclerosis (SSc) and the other half had systemic lupus erythematosus (SLE). They were matched to cases 3:1 for age (within 2 years) and gender.
Results: 30 patients had received SBI (mean age 47.9, 100% female). 12 had a diagnosis of depression, 6 of fibromyalgia and 3 of CFS. Implant rupture was not associated with any of these (p=1).There was no difference in the incidence of depression (p=1), fibromyalgia (p=0.76) or CFS (p=0.3) between cases and SLE controls. When compared with SSc controls, there were significantly more patients with fibromyalgia and/or CFS in the case group (20.0% of cases vs 2.2% of SSc controls, p=0.01) but no difference in depression (p=0.12).
Discussion: Fibromyalgia and CFS are more common in patients with silicone implants than SSc controls but not SLE controls. Prospective study of development of depression, fibromyalgia and CFS recipients of SBI are required.

AUTO1-0633
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

CLINICOPATHOLOGIC STUDIES IN LAMBS REPETITIVELY INOCULATED WITH ALUMINUM ADJUVANT CONTAINING PRODUCTS

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Background

The use of aluminum-containing vaccine adjuvants is widespread in the Spanish small ruminant industry. These compounds were related to an episode of vaccine adverse reactions which gave rise to a process known today as the ovine ASIA syndrome.

Method

An in vivo model of this syndrome was established. Eighty-four lambs were selected, divided into three groups (n=28 each) and submitted to an intensive inoculation program with: i) Vaccines containing aluminum hydroxide as adjuvant; ii) The adjuvant only; iii) PBS. Nineteen inoculations were performed during 15 months. A comprehensive in vivo follow-up was performed, including clinical examinations and behavioral and cognitive tests. After euthanasia, the pathology of different tissues was studied grossly, microscopically and by electron microscopy. The presence of aluminum in tissues was studied by energy dispersive X-ray spectroscopy, graphite furnace atomic absorption spectroscopy and lumogallion fluorescent staining.

Results

Animals in the vaccinated and adjuvant-inoculated groups presented persistent injection-site granulomas with intramacrophagic aluminum. Persistency was higher in the vaccinated group ($p<0.001$), reaching 15 months in some cases. There was translocation of aluminum to the regional lymph nodes ($p<0.001$) and lumbar spinal cord ($p<0.001$). Vaccinated and adjuvant-inoculated animals showed an increase in aggressive interactions ($p<0.001$) and stereotypies ($p<0.001$) and a decrease in affiliative interactions ($p<0.001$) when compared with the control group. Differences were more marked with higher number of doses applied.

Conclusion

Repetitive inoculation of aluminum-hydroxide only or combined into commercial vaccines to experimental lambs induces highly persistent injection site granulomas, accumulation of aluminum in distant tissues and changes in the inter-individual interaction patterns.

AUTO1-0098
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

SYSTEMIC SCLEROSIS AND EXPOSURE TO HEAVY METALS

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Background

To date, no investigators have yet assessed the risk of SSc in patients exposed to heavy metals.This case control study assessed: 1) the relationship of systemic sclerosis (SSc) related to exposure to heavy metals; and 2) the risk of SSc related to occupational exposure in male and female patients

Method

From 2005 to 2008, 100 patients with a definite diagnosis of SSc were included in the study; 3 age, gender, and smoking habit matched controls were selected for each patient. All SSc patients and controls underwent detection and quantification of heavy metal traces in hair samples, using multi-element inductively coupled plasma mass spectrometry (ICP-MS).

Results

SSc patients exhibited higher median levels of the following metals: antimony ($p = 0.001$), cadmium ($p = 0.0003$), lead ($p = 0.02$), mercury ($p = 0.02$), molybdenum ($p = 0.04$), palladium ($p < 0.0001$) and zinc ($p = 0.0003$). A marked association between SSc and occupational exposure was further found for: 1) antimony ($p = 0.008$) and platinum ($p = 0.04$) in male patients; and 2) antimony ($p = 0.02$), cadmium ($p = 0.001$), lead ($p = 0.03$), mercury ($p = 0.03$), palladium ($p = 0.0003$) and zinc ($p = 0.0001$) in female patients

Conclusion

The results show the impact of occupational risk factors in the development of SSc for: antimony, cadmium, lead, mercury, molybdenum, palladium and zinc. Thus, occupational exposure should be systematically checked in all SSc patients at diagnosis. Finally, the association between SSc and occupational exposure may be variable according to patients' gender.

AUTO1-1081
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

AUTOANTIBODIES IN PATIENTS SUSPECTED OF ADVERSE EFFECT OF HPV-VACCINATION

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The ability to prevent HPV-related cancer by a vaccine is undeniably important, but heterologous reactions to antigens such as those delivered through vaccination is an inherent risk and may result in autoimmunity and perhaps in autoimmune disease. It has been pointed out that there are a high number of matches between the HPV-vaccine and the human proteome making autoimmune cross-reactions very likely. In recent years, case series describing patients with side effects potentially attributed to the HPV-vaccines have emerged from several countries. The symptoms described in these publications include chronic excessive fatigue and pronounced autonomic dysfunction, coupled with severe headache, disordered sleep, cognitive dysfunction, gastrointestinal discomfort, hyperactive bladder dysfunction, widespread muscular pain, and muscular dysfunction. The clinical presentation resembles that seen in chronic fatigue syndrome and complex regional pain syndrome and antibodies against G-protein coupled receptors have been demonstrated in both syndromes possibly accounting for the associated symptoms.
In Denmark approximately 630.000 females aged 12 to 27 years have received HPV-vaccination as part of the subsidized vaccination program. The Danish Health authorities have received more than 2,000 reports on suspected side-effect of which more than 1,000 were classified as being serious. Centers for such patients have been established i the five regions of Denmark and in the Capital Region we have seen almost 800 patients at present. Their mean age was 22+/-6 years at vaccination i.e. most of the patients belong to the "catch-up" vaccine group. We have demonstrated postural orthostatic tachycardia syndrome in a 56% of the patients and compared to vaccinees without symptoms they had a much higher score on symptoms from the autonomic nervous system (52.5+/-13 versus 2.8+/-2.5). We could demonstrate agonistic autoantibodies against G-protein coupled receptors in 93% of the symptomatic patients, in 30% of the asymptomatic vaccinees, and in 15% of the unvaccinated. We have found a possible basis for molecular mimicry between the content of the vaccine and the human proteome. The nature of the antibodies makes it likely that they are responsible for the symptoms and using specific antagonists has a positive clinical effect.
HPV-vaccination has had a widespread use for the purpose of preventing precancerous lesion and eventually cancer of the cervix. A number of relatively rare, possible side-effects have been reported giving rise to often severely in capacitating symptoms most likely ascribed to an autoimmune condition primarily affecting the autonomic nervous system. The condition bears a close resemblance to Chronic Fatigue/Myalgic Encephalopathy with a 90% overlap in symptoms.

AUTO1-0152
AUTOIMMUNE SYNDROMES INDUCED BY ADJUVANTS (ASIA)

IS MOLD AND DAMPNESS HYPERSENSITIVITY SYNDROME (DMHS) A PREDISPOSING FACTOR FOR THE DEVELOPMENT OF ASIA AFTER VACCINATION WITH PANDEMRIX AND HPV VACCINES?

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Dampness and Mold Hypersensitivity Syndrome (DMHS) is very prevalent in Finland. This disease is not considered a disease at all, and the patients receive neither social security nor proper medical care. Continuous or cumulative exposure to indoor air toxins emitted by growing dampness microbiota and volatile organic compounds derived from damaged constructions can cause a great plethora of symptoms. When the disease becomes chronic, the symptoms are no more reversible which may cause disability in young ages. In about half of chronic DMHS a multiple chemical sensitivity (MCS) will develop (Valtonen, Fr. Immunol 2017). According to our estimation approximately 20000 of school children might have mild or moderate DMHS, and 2000-5000 children have advanced DMHS with MCS.
Because DMHS is not considered as a disease, children who present with symptoms related to DMHS, are considered healthy, and therefore receive a full scheme of vaccination.
We initiated a retrospective double blind study to investigate whether post-vaccination neurological sequelae, such as postural orthostatic tachycardia (POTS), pediatric acute onset neuropsychiatric syndrome (PANS), chronic fatigue syndrome (CFS) or complex regional pain syndrome (CRPS) is related to DMHS. At the time of this communication we have tagged 45 families but the number of cases is nearly 100. A questionnaire through social media was sent to families. The data will be collected by December 2017 and analyzed in January-February 2018.
We hope get an answer to the question whether or not DMHS might be an independent contributor to the development of devastating neurological complications in vaccinated Finnish schoolchildren.

AUTO1-0716
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

CORRELATION BETWEEN CLINICAL AND LABORATORY MARKERS AND DEPRESSION IN A PORTUGUESE SYSTEMIC LUPUS ERYTHEMATOSUS COHORT – FATIGUE AND QUALITY OF LIFE AS THE MAJOR PLAYERS

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects a large number of people throughout the world. Depression is a frequent co morbidity and a supplementary burden to the lupus patients. Our aim was to detected correlations between clinical presentation, laboratory tests, and depressive symptoms, and to identify psychosocial factors of this relationship.

Method

A cohort of lupus patients was screened for the presence of depressive symptoms (HADS). Assessment included fatigue (CFS & FSS), sleep and quality of life (SF-36 & PSQI). Scores from these assessments were correlated with lupus clinical profiles and laboratory test values.

Results

The prevalence of depression in the SLE patient cohort was 41.7 %, as measured by the HADS. The study identified that pain ($p = 0.001$), body mass index ($p = 0.026$), Chalder's fatigue scale ($p < 0.001$), fatigue severity scale ($p < 0.001$), and anxiety ($p = 0.001$) are all positively correlated with depression in SLE patients. Multivariant scrutiny of the clinical and psychosocial characteristics identified the fatigue severity scale ($p = 0.026$), SF-36 physical function ($p = 0.040$), physical role function (0.030), and mental health ($p = 0.002$) as the best indicators directly correlated with depression for the SLE cohort.

Conclusion

These results reveal the influence of physical manifestations of lupus as well as decreased physical and mental function, on depression. Fatigue is the strongest factor correlated to depression in SLE patients in the cohort. Both physical and sociopsychological aspects likely contribute to the depression and anxiety in lupus.

AUTO1-0272
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

TOWARDS MOLECULAR INSIGHTS INTO PSYCHIATRIC DISORDERS USING AFFINITY PROTEOMICS

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Background

In the recent years, studies have shown a correlation between higher levels of autoantibodies and the frequency of autoimmune disease in patients with psychiatric disorders compared to healthy individuals. In this study we used a targeted affinity proteomics approach to investigate the autoantibody repertoire of samples obtained from patients diagnosed with various psychiatric disorders and compared these with samples of healthy volunteers.

Method

In this study several psychiatric disorder associated cohorts, with different sample types have been used to study the autoantibody repertoire. In total we analysed more than 600 serum and 130 brain tissue samples in a first discovery phase. Based on this and previous in-house and external published studies of autoantibodies within psychiatry we selected 224 protein fragments from the Human Protein Atlas with a length of roughly 80 amino acids. Autoantibody profiling was performed using suspension bead array technology and IgG reactivity was measured in patients and controls.

Results

Our findings indicate altered immune response in patients with chronical mental illness compared to healthy controls. In our study we identified potential predictive autoantibody signatures, presented with higher IgG reactivity in patients compared to healthy control samples.

Conclusion

With our approach we were able to profile autoantibody repertoires in patients with psychiatric disorders. By further validating these putative autoimmunity targets, we could gain insights into the autoantigens associated to chronical mental illnesses.

AUTO1-0476
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

PROFILING THE IGG REPERTOIRE IN CSF FROM PATIENTS WITH FRONTOTEMPORAL DEMENTIA

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Background

Frontotemporal dementia (FTD) is characterized by neuronal loss mainly in the frontal and temporal lobes. Approximately 40% of patients have genetic mutations and a family history of disease while the majority of patients present a sporadic onset. The underlying pathophysiology is unknown but the loss of a specific type of neuron, namely the spindle neurons, and increased prevalence of other autoimmune disorders suggest that autoimmune components could be involved.

Method

We have performed an extensive profiling of CSF IgG reactivity in patients with FTD as well as non-neurological and neurological controls from two independent sample cohorts. First, 78 samples (36 patients and 39 at-risk relatives) from the first cohort were profiled for reactivity towards 8000 antigens using microarrays with human protein fragments. In addition, a more extensive analysis was made for eight of the samples using a high-density array with 21000 antigens. This was followed by a directed analysis of reactivity to 370 proteins with higher mRNA levels in brain compared to other human tissues using both the initial 78 samples as well as 13 additional FTD patients, 79 patients with Alzheimer's disease and 49 controls.

Results

In total, 143 antigens were selected for further characterisation. Among these was the enzyme methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2-like (MTHFD2L) that showed IgG reactivity in all patients and at-risk relatives in the initial cohort. The findings are currently followed up in an independent sample material including in total more than 200 CSF samples.

Conclusion

The presented study provides suggestions of novel autoimmune targets associated to FTD.

AUTO1-0308
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

THE AIM OF THIS RESEARCH, TO KNOW THE IMPACT OF THE PSYCHOLOGICAL ASPECT OF PHYSIOLOGICAL ADAPTATIONS TO A PATIENT'S HEALTH.

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Background

Pathophysiology of leukemia and its effect on autoimmune immunity - Algerian experience -a model

The aim of this research, which under the title "Pathophysiology of leukemia and its effect on autoimmune immunity - Algerian experience -a model" to address the definition of self-diagnosed HIV types and methods in addition to knowing the impact of the psychological aspect of physiological adaptations on the health of the patient blood cancer, and in the latter to reach acceptable recommendations.
keywords:
Pathophysiology , leukemia , effect , autoimmune immunity .

Method

The descriptive approach will follow the analytical work by taking a sample i am by experimentation by category of infected blood cancer, through the instrument of the Form

Results

The results of the study will appear in the analysis of the data at the end of the research, which will be sent to you when you accept the summary under the title "Pathophysiology of leukemia and its effect on autoimmune immunity - Algerian experience -a model"Basheer Ben Nasser Hospital

Conclusion

In the results show us that the PATHOPHYSIOLOGY has great impact on the patient's condition which interfere with several factors and thus led to the deaths of many cases in Algeria

AUTO1-0695
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

HASHIMOTO'S ENCEPHALOPATHY - A REVIEW OF SUSPECTED CULPRITS IN DISEASE PATHOGENESIS

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Background

Psychiatry appears to be one of the most undeciphered fields in medicine. The majority of psychiatric diagnoses are based on symptomatology, rather than specific clinical markers, representing the yet poor understanding of the bio-pathological processes at the basis of mental illness. However, with the advance of research during recent decades, a novel factor has been suggested as the culprit behind various psychiatric pathologies – the human immune system.

Method

Herein we review the current evidence regarding the role of autoimmune processes in the pathogenesis of various psychiatric illnesses.

Results

We address psychiatric manifestations of classical autoimmune diseases; the emerging entity of autoimmune encephalitis, which often presents with psychiatric symptoms; a potential role of autoimmunity in schizophrenia and mood disorders; a possible association of autism with autoimmunity; and finally, findings regarding immune-inflammatory processes in dementia.

Conclusion

While much of data concerning the role of autoimmune processes in psychiatric illnesses is rather preliminary and requires substantial further investigation, it seems safe to ascertain that future decades entail significant discoveries interlinking the fields of immunology and psychiatry.

AUTO1-0055
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

BIOMARKERS OF AUTOIMMUNITY IN ALZHEIMER'S DISEASE: THE ROLE OF THE GUT MICROBIOME, FOOD PROTEINS AND PATHOGENS

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Alzheimer's disease (AD) is currently responsible for 60 to 80% of dementia cases worldwide. Apolipoprotein E gene amyloid oligomer formation, human pathogens, toxic chemicals and diet are all implicated in its etiology. Due to this multifactorial nature, we measured IgG and IgM antibodies against neuropathologic target proteins, infectious agents, and cross-reactive food proteins in AD patients and controls. Statistical analysis using Pearson's correlation was performed. For IgG the correlation between antibody to beta-amyloid peptide and neuronal proteins was highly significant with $p < 0.0000$ and coefficients from 0.93 – 0.98. In relation to pathogens or their antigens, this correlation was significant for LPS, HSV-1, HHV-6, streptozymes, S. mutans, and B. burgdorferi with $r = 0.60$, 0.49, 0.48, 0.46, 0.39, and 0.36 respectively, while for the others r was less than 0.35. For IgM antibody, the correlation between beta-amyloid peptide antibody and the other four tested neural antigens again was highly significant with $r = 0.73 – 0.94$; for LPS $r = 0.71$, and for streptozymes $r = 0.72$. The correlation between IgM antibody to beta-amyloid peptide and all tested pathogens was very significant with $r = 0.59 – 0.77$. These correlations indicate that these antibodies could be used as biomarkers of autoimmunity in AD. We propose that overproduction of LPS by a disturbed gut microbiome can open the blood barrier, allowing circulating infectious agents, food and other cross-reactive antibodies to enter the nervous system, where immune complex formation and pro-inflammatory cytokine production contribute to the formation of amyloid plaque. This can lead to progressive synaptic dysfunction, neuronal loss, and AD. We suggest that scientists should look for multiple environmental causes of AD, and stop looking for a single cause and assuming that removing one cause is going to stop the onset and lifetime progression of Alzheimer's disease.

AUTO1-0588
AUTOIMMUNITY AND PSYCHIATRIC DISEASES

THE IMMUNOREGULATORY EFFECTS OF PSYCHOLOGICAL STRESS MODIFICATION AND DAILY MODERATE EXERCISE WITH TAI CHI INTERVENTION SUGGEST EFFICACY AS AN ADJUNCT THERAPY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Exercise and stress modification programs are currently underemphasized to systemic lupus erythematosus (SLE) patients because comprehensive immunological characterization has not been examined and conventional regimens have not been established. We previously demonstrated that daily moderate exercise is beneficial and psychosocial stress induction is detrimental to disease progression in a lupus nephritis mouse model. The objective of this study was to translate these results using a pilot cohort of SLE patients.

Method

Active SLE patients (N=12) were enrolled in a daily Tai Chi program for 2.5 months. Participants scored low on a physical activity questionnaire and above average on the perceived stress scale at enrollment. Data were collected at baseline and throughout the study via questionnaires to access physical activity and stress levels, activity trackers (Fitbit), and blood draws.

Results

Questionnaires confirmed a significant reduction in perceived social stress and an increase in combined metabolic equivalent of task (MET) and overall physical activity compared to baseline levels. Fitbit data showed a significant increase in steps, distance, and activity calories without changes in body mass index or vigorous activity levels. Serum sample analysis showed a decrease in cortisol levels and a reduction in cytokine expression of IL-6 (23%), IL-8 (30%), TNF-α (11%), IFN-ɣ (21%), and MCP-1 (20%) with Tai Chi intervention. No significant changes were observed in non-Tai Chi SLE patients.

Conclusion

Moderate exercise and stress management have detectable immunosuppressive properties; thus establishing daily Tai Chi as a viable adjunct therapy alongside current pharmacological interventions to treat the chronic, systemic inflammation associated with SLE.

AUTO1-0558
AUTOIMMUNITY IN THE BRAIN

ELUCIDATING THE MECHANISMS OF CNS ENTRY AND THE ROLE OF TH17 CELLS IN AUTOIMMUNE BASAL GANGLIA ENCEPHALITIS.

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Background

Group A Streptococcus (GAS) infections in children cause autoimmune basal ganglia encephalitis (BGE) that manifests with **motor** [Sydenham's chorea] and **psychiatric** [Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)] symptoms. Autoantibodies that recognize neuronal targets are found in sera from SC/PANDAS children. These autoantibodies elicit behavioral abnormalities when infused into rodent brains or administered intravenously (i.v.) to rodents. We have shown that an intranasal (i.n.) route of GAS infection leads to production of Th17 cells in nasal-associated lymphoid tissue. Th17 cells migrate from the nose into the brain and their presence correlates with BBB breakdown, extravasation and brain deposition of antibodies and synaptic dysfunction.

Method

Here, we examine the mechanisms by which GAS-specific Th17 cells enter the CNS in mice and determine the role that Th17 cells and autoantibodies play in BBB damage, neuroinflammation and circuit dysfunction.

Results

We find that two chemokines are expressed in the olfactory epithelium and bulb when Th17 cells enter the CNS. We are currently testing the role that these chemokines play in this process using genetic studies in mice. We find that genetic ablation of two chemokine receptors that bind to chemokines upregulated in the CNS leads to a significant reduction in T cell entry into the CNS. Using mice that lack Th17 cells and undergo GAS infections, we find that, although the number of T cells is reduced, Th1 cells enter the CNS and produce neurovascular and synaptic damage.

Conclusion

Therefore, both Th17 and Th1 cells are important for disease pathogenesis in post-infectious BGEs.

AUTO1-0155
AUTOIMMUNITY IN THE BRAIN

MOLECULAR PATHOGENICITY OF ANTI-NMDA RECEPTOR AUTOANTIBODIES FROM PSYCHOTIC PATIENTS: NEW LIGHTS AT THE SINGLE MOLECULE LEVEL

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Background

The flourishing identification of circulating autoantibodies against neuronal receptors in neuropsychiatric disorders has fostered new conceptual and clinical frameworks. Circulating autoantibodies against glutamatergic N-methyl-D-aspartate receptor (NMDAR-Ab) have in particular been reported in a proportion of patients with psychotic disorders, raising hopes for more appropriate treatment for these antibody-positive patients. However, based on conventional cellular approaches the prevalence and molecular impact of these NMDAR-Ab from psychotic disorders have been debate.

Method

We used a unique combination of single molecule-based imaging, classical confocal imaging, electrophysiological, and molecular biology approaches in hippocampal cellular networks to test the impact of purified human autoantibodies.

Results

Using this experimental combination, we will here evidence the presence of circulating autoantibodies against glutamate NMDA receptor (NMDAR-Ab) in both schizophrenic and first psychosis episode patients, further discussing the outcomes of the different available cell-based assays. In addition, we will describe how NMDAR-Ab from psychotic patients, but not from healthy subjects or psychiatric patients without psychosis, alter the NMDAR signaling. Indeed, imaging at the single receptor level within live brain tissue shed unexpected lights on the molecular disturbance induced by autoantibodies, highlighting the need for molecular investigations to fully dissect the pathogenic potential of these autoantibodies.

Conclusion

Together, single molecule imaging unveiled that NMDAR-Ab from psychotic patients profoundly alter NMDAR synaptic transmission in a non-canonical pathway, supporting a pathogenically relevant role in autoimmune psychosis.

AUTO1-0584
AUTOIMMUNITY IN THE BRAIN

NEUROIMMUNE INTERACTION IN SPINO-CEREBELLAR ATAXIA

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Background

To report the clinical and immunological characteristics of 22 new patients with glial fibrillar acidic protein (GFAP) autoantibodies.

Method

We recruited 282 patients with suspected neurological autoimmune disease at the Catholic University of Rome. Patients' serum and cerebrospinal fluid (CSF) samples were tested for neural autoantibodies by immunohistochemistry on mouse and rat brain sections, by cell-based assays (CBA) and immunoblot. GFAP autoantibodies were detected by immunohistochemistry and their specificity confirmed by CBA using cells expressing human GFAPα and GFAPδ proteins, by immunoblot and immunohistochemistry on GFAP-/- mouse brain section

Results

Serum and/or CSF IgG of 22/451 (5%) patients bound to human GFAP, of which 22/22 bound to GFAPα, 14/22 to both GFAPα and GFAPδ and none to the GFAPδ isoform only. The neurological presentation was: meningoencephalomyelitis or encephalitis in 10, movement disorder (choreoathetosis or myoclonus) in 3, anti-epileptic drugs (AED)-resistant epilepsy in 3, cerebellar ataxia in 3, myelitis in 2, optic neuritis in 1 patient. Coexisting neural autoantibodies were detected in five patients. Six patients had other autoimmune diseases. Tumours were found in 3/22 patients (breast carcinoma, 1; ovarian carcinoma, 1; thymoma, 1). Nineteen patients were treated with immunotherapy and 16 patients (84%) improved. Histopathology analysis of the leptomeningeal biopsy specimen from one patient revealed a mononuclear infiltrate with macrophages and CD8+ T cells.

Conclusion

GFAP autoimmunity is not rare. The clinical spectrum encompasses meningoencephalitis, myelitis, movement disorders, epilepsy and cerebellar ataxia. Coexisting neurological and systemic autoimmunity are relatively common. Immunotherapy is beneficial in most cases.

AUTO1-0175
AUTOIMMUNITY IN THE BRAIN

EPILEPSY AMONG SYSTEMATIC LUPUS ERYTHEMATOSUS PATIENTS: INSIGHTS FROM A LARGE DATABASE ANALYSIS

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Background

Epilepsy is characterized by a relevant epidemiological and clinical burden. In the extant literature, an increased risk of seizures has been described in several inflammatory/autoimmune disorders, including systematic lupus erythematosus (SLE). However, so far, relatively few and small size-based studies have been conducted. We aimed to investigate the link between seizure and SLE utilizing a large sample of subjects and extensive data analysis.

Method

Patients with SLE were compared with age and sex-matched controls regarding the prevalence of epilepsy in a cross-sectional study. Chi-square and t-tests were used for univariate analysis and a logistic regression model was used for multivariate analysis. The study was performed utilizing the medical database of Clalit Health Services.

Results

The study included 5,018 patients with SLE and 25,090 age- and gender-frequency matched controls. The proportion of epilepsy was found significantly higher among SLE patients (4.03% vs 0.87%, p<0.001). At the logistic regression, adjusting for multiple confounding factors, older age (≥70 years) resulted as negative predictor (OR 0.42 [95%CI 0.27-0.62], p <0.001)), whereas the presence of SLE was a positive predictor of epilepsy (OR 4.70 [95%CI 3.94-5.82], p <0.001). Interaction between SLE and elderly age resulted in high OR for epilepsy, of 5.47 (95%CI 2.53-11.9).

Conclusion

Our study confirms the higher prevalence of epilepsy in SLE patients. Physicians should be aware of such findings and have a lower threshold for suspecting epileptic seizures in these patients. Further studies are needed to better elucidate the mechanisms by which SLE favors the insurgence of seizures.

AUTO1-0205
AUTOIMMUNITY IN THE SKIN

NEUTROPHIL ADHESION IS REQUIRED FOR PROTEASE ACTIVITY IN VIVO IN AN EXPERIMENTAL AUTOIMMUNE EPIDERMOLYSIS BULLOSA ACQUISITA

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Background

Uncontrolled proteolysis of neutrophil proteases is responsible for tissue damage in many chronic situations such as autoimmune diseases. However, mechanisms how these enzymes mediate tissue damage *in vivo* remain unclear. By using fluorescence resonance energy transfer (FRET) sensors, we visualized site-specific neutrophil elastase (NE) activity on immune complex (IC) activated neutrophils on the single-cell level *in vivo*.

Method

The performance of specific FRET sensor (NEmo-2) was analyzed on neutrophils in the context of a living cell-based model. An autoimmune experimental model of epidermolysis bullosa acquisita (EBA) was used to confirm these data. Donor (D) fluorescence and sensitized acceptor (A) emission were imaged and D/A ratio were calculated.

Results

In EBA mouse model, where proteinase inhibitors are present in the locally inflamed tissue, neutrophils were activated by IC in the presence of the alpha-1 antitrypsin (A1AT) *in vivo*. D/A ratio signal of neutrophils in anti-mCOL7-treated mice were found to be significantly higher than in those which had received a corresponding irrelevant antibody, suggesting that IC-mediated activation induces extracellular elastase enzyme activity. By contrast, no such increase could be induced when *Cd18*$^{-/-}$ neutrophils were transferred under the same conditions indicated by their comparable D/A ratios under anti-mCOL7 and isotype-antibody treatment.

Conclusion

IC-induced neutrophil adhesion created an enclosed protected space between the cell and its target structure where proteinases can execute their tissue-damaging effect. Since IC-induced neutrophil adhesion represents an indispensable step tissue damage of many diseases, our findings may facilitate the development of novel strategies for the treatment of such disorders.

AUTO1-0356
AUTOIMMUNITY IN THE SKIN

TH1-LIKE INITIATING- AND RECALL-RESPONSES TO MELANOCYTES IN GROWING FEATHERS OF SMYTH CHICKENS WITH AUTOIMMUNE VITILIGO

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Background

Vitiligo is a depigmentation disorder driven by the autoimmune targeting and elimination of melanocytes in the skin. The Smyth line of chicken (SL) is a well-established animal model for spontaneous autoimmune vitiligo, providing opportunities to gain insight into disease etiology.

Method

To examine immunological activities responsible for SL-vitiligo initiation and progression, growing feather (GF; target tissue) samples were taken twice per week from 14 SL chickens starting at 1 day post-hatch and continuing until 16 weeks of age. Selected chickens were also monitored for visible depigmentation of feathers (indicative of vitiligo onset) for the duration of the study. Single cell suspensions prepared from GF pulp were immunofluorescently stained for phenotypic leukocyte population analysis by flow cytometry. Additionally, pulp tissue was subjected to targeted gene-expression analysis by qRT-PCR.

Results

Independent of age, T- and B-cell infiltration was observed one- and two-weeks prior to vitiligo onset, respectively. While both CD4+ and CD8+ T cells reached peak levels at vitiligo onset, levels of CD4+ T helper cells declined gradually thereafter whereas those of CD8+ cytotoxic T cells remained elevated until depigmentation (melanocyte loss) was complete. Gene expression analysis suggested active recruitment (CCL19, CCR7) of lymphocytes prior to onset and a sustained Th1-like gene signature (IFN-γ, FASLG, GZMA) throughout disease progression. A similar response pattern was observed when feather-derived melanocytes were injected into the pulp of completely depigmented GF and the recall response monitored for 7 days.

Conclusion

The SL-vitiligo model provides unique opportunities to dissect mechanisms underlying loss of tolerance and autoimmune disease expression and progression.

AUTO1-0502
AUTOIMMUNITY IN THE SKIN

BLOCKADE OF THE NEONATAL FC RECEPTOR HAS THERAPEUTIC EFFECTS IN MURINE EPIDERMOLYSIS BULLOSA ACQUISITA

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Background

Epidermolysis bullosa acquisita (EBA) is a prototypic autoimmune disease caused by autoantibodies against type VII collagen (COL7) and clinically characterized by inflammation and subepidermal blistering predominately in the skin. EBA is notoriously difficult to treat. Hence, there is a so far unmet medical need to develop safe and effective treatment options for EBA. The neonatal Fc receptor (FcRn) has emerged as a potential therapeutic target because mice lacking FcRn were protected from experimental EBA. However, whether therapeutic FcRn blockade has any effect on clinical disease is unknown.

Method

To address this knowledge gap, we immunized mice with murine COL7, allocated individual mice to an anti-FcRn monoclonal antibody (“4470”) or isotype control treatment, when EBA skin lesions affected >2% of the body surface area, and evaluated the clinical and immunological effects.

Results

In isotype controls, clinical disease severity, expressed as affected body surface area, increased by 50% during the 4-week observation period. In contrast, with 4470 treatment, clinical disease significantly improved as soon as one week after starting the treatment. This effect was maintained and became more evident over the course of the experiment. Clinical improvement was associated with the lowering of circulating and tissue-bound autoantibody concentrations. No effect of 4470 treatment on the function of myeloid cells was observed.

Conclusion

In summary, pharmacological blockade of FcRn has therapeutic effects in murine EBA. Hence, targeting FcRn seems a promising therapeutic strategy for the treatment of EBA and other autoantibody-mediated diseases. These data now warrant the exploration of FcRn-targeting strategies in patients.

AUTO1-0440
AUTOIMMUNITY IN THE SKIN

DIFFERENTIAL EFFECT OF PHOSPHODIESTERASE-4 INHIBITION ON SKIN AND MUCOSAL LESIONS IN EXPERIMENTAL ANTI-LAMININ 332 MUCOUS MEMBRANE PEMPHIGOID

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Background

The immunobullous disease mucous membrane pemphigoid (MMP) is characterized by autoantibodies against the dermal-epidermal-junction and a predominant mucosal involvement. Reactivity against laminin332 (Lam332), a heterotrimer consisting of 3 laminin chains, is found in one third of MMP patients. Major clinical and immunopathological characteristics of the human disease including both mucosal and skin lesions are recapitulated in the recently established antibody-transfer-induced-mouse model for anti-Lam332-MMP in adult mice. As the treatment of anti-Lam332-MMP still relies on high-dose corticosteroids, there is a high unmet need for new and more specific treatment. Phosphodiesterase-4 (PDE4) inhibition has previously been shown to be effective in patients with psoriasis vulgaris and Behcet's disease.

Method

A specific PDE4 inhibitor, roflumilast, was applied in a prophylactic approach in the anti-Lam332-MMP mouse model, in two independent blinded experiments with 5mg/kg/day p.o..

Results

Roflumilast significantly reduced oral lesions compared to vehicle-treated mice as quantified by endoscopy ($p=0.029$), whereas a significant increase in skin lesions was observed ($p<0.0001$). Direct immunofluorescence microscopy showed linear deposits of IgG and C3 in both tissue types. In contrast, in lesional biopsies, the number of inflammatory cells was significantly decreased in the buccal mucosa, but not in the skin, of roflumilast-treated compared to vehicle-treated mice ($p=0.007$, $p=0.1523$). No differences were detected in conjunctival involvement and body weight between roflumilast-treated and control mice.

Conclusion

A transcriptome analysis of skin and mucosal lesions validated by RT-PCR and Western blotting will help to identify the key molecules responsible for the differential effect of PDE4-inhibition on antibody-mediated tissue destruction in skin and mucosa.

AUTO1-0231
B AND T CELLS

EXPRESSION OF PTH RECEPTOR AND EFFECTS OF PARATHYROID HORMONE ON THE ACTIVATION OF B LYMPHOCYTES IN PATIENTS WITH PRIMARY SJOGREN SYNDROME

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Background

Some clinical studies have determined that patients with hyperparathyroidism may display monoclonal gammopathies and autoimmune diseases, and after hyperparathyroidism treatment, clinical and biological recovery is evidenced. However, the biological role of Paratohormone (PTH) on B lymphocytes in autoimmune diseases has not been clearly established. Our aim was to evaluate the expression of the PTH receptor (PTH1R) in the membrane of mature B lymphocytes in patients with primary Sjogren's syndrome (pSS) and SLE patients.

Method

By flow cytometry, we evaluated the expression of PTH1R in mature B cells from SLE (n=6, 39.3±13.5 and pSS patients (n=10, 64,5±7.79) as well as healthy controls (HC) ; by determining the percentages of CD19+(J3-119), IgD (IgD26) and CD38(LS198-4-3), (Bm1-Bm5 classification), and addition to PTH1R (polyclonal) stained by PE-goat anti-rabbit IgG.. Statistical analysis was performed using the Anova or Kruskal Wallis for comparisons between groups and Tukey o Dunnett for peer comparisons.

Results

Expression of PTH1R was significantly higher in almost all the subsets of mature B cells (except for Bm5) in patients with pSS compared to SLE and HC. These differences were more marked in Bm2 (% of PTH1R expression: 1.86 in HC *vs.* 24.87 in pSS; p= 0.006) and Bm2' (% of PTH1R expression:2.06 in HC *vs.* 68.58 in pSS; p=0.001) subsets **(Table**

1). SLE patients displayed the same pattern that HC.

Table 1. Expression of PTHR1 in mature B cells (from Bm1 to Bm5) from patients with SLE and pSS compared to healthy controls (significant differences are highlighted).

Phenotype B cells	Attribute	Health Control	LES - Mean	pSS - Mean	*P* value
Bm1	% Cells	11.52 (8.06-12.38)	5.43 (4.87-7.64)	9.98 (5.41-41.24)	0,1718
	% PTH1R	3 (2.97-3.59)	4.42 (1.66-4.93)	10.48 (5.19-34.94)	0,0176
	X mean	6.59 (6.24 - 7.26)	4.5 (3.1-8.46)	4.53 (2.27-10.26)	0,8321
Bm2	% Cells	55.9 ± 9.22	47.78 ± 10.17	31.2 ± 19.8	0,0097
	% PTH1R	1.86 (0.76-5.96)	3.64 (1.88-4.27)	24.87 (5.53-73.28)	0,0067
	X mean	6.16 (2.63-8.98)	6.66 (3.37-8.91)	8.14 (6.52-10.63)	0,409
Bm2'	% Cells	4.31 (3.53-5.64)	2.95 (0.73-4.31)	0.67 (0.28-3.28)	0,409
	% PTH1R	2.06 (1.2-7.83)	11.01 (7.69-13.51)	68.58 (12.5-100)	0,0177
	X mean	8.12 (7.1-15.54)	5.72 (4.59-10.49)	10.98 (9.96-37.1)	0,1582
Bm3/4	% Cells	3.18 (1.89-4.37)	3.48 (0.38-12.81)	4.03 (1.21-8.23)	0,409
	% PTH1R	3.76 (0.61-6.17)	2.95 (1.77-3.33)	39.74 (16.32-100)	0,003
	X mean	5.49 (4.24-12.05)	4.74 (3.76-5.23)	7.96 (4.51-40.96)	0,2305
Early Bm5	% Cells	14.91 ± 5.01	23.75 ± 8.46	16.03 ± 11.62	0,1988
	% PTH1R	1.98 (0.92-3.23)	1.8 (1.17-2.59)	10.40 (3.21-71.01)	0,0065
	X mean	3.93 (3-4.59)	3.94 (2.76-4.86)	7.25 (3.69-8.68)	0,2691
Late Bm5	% Cells	7.73 (7.56-11.32)	10.73 (7.96-15.79)	18.81 (11.19-21.29)	0,409
	% PTH1R	1.8 (0.99-5.24)	1.69 (1.56-9.86)	10.08 (4.5-24.32)	0,0607
	X mean	3.93 (2.74-4.29)	3.07 (2.01-4.26)	2.68 (2.15-4.18)	0,522

Conclusion

Our findings show that PTHR1 is highly expressed on B cells from pSS, and may contribute to their pathogenesis. The effects of PTH on B-cell survival, proliferation and immunoglobulins production are currently under evaluation.

AUTO1-0972
B AND T CELLS

CLINICAL OUTCOMES IN THE TREATMENT OF AUTOIMMUNE MUCOCUTANEOUS BLISTERING DISEASES: A LONG TERM SINGLE CENTER EXPERIENCE

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Background

Autoimmune mucocutaneous blistering diseases (AMBDs) represent a medical challenge with lack of data on long-term treatment outcomes.

Method

We assessed retrospectively long term results on AMBDs patients treated in our Department between January 2008 and January 2018.

Results

We reviewed 145 patients: 113 (77.9%) had Pemphigus Vulgaris, 27 (18.6%) Mucous Membrane Pemphigoid, 3 (2.0%) Lichen Planus Pemphigoides, 2 (1.5%) Bullous Pemphigoid. First-line conventional treatment included corticosteroids and immunosuppressants: 85 patients (58.6%) reached complete clinical remission off therapy, and 20 (13.8%) partial or complete remission on therapy.
Rituximab and/or IVIgG were used in 40 (27.6%) cases unresponsive to conventional treatments and/or with contraindications to corticosteroids or severe side effects.

Six patients (4.1%) received Rituximab, eight patients (5.5%) received Rituximab and IVIgG because of the severity of the disease, and eight patients (5.5%) received IVIgG and conventional immunosuppressive therapy.

The following side effects were recorded: one case of aseptic meningitis, and one with deep vein thrombosis in patients treated with IVIgG; two cases of laryngospasm, one with atrial fibrillation and one with dyspnea in patients treated with Rituximab. Approximately 40.0% of patients treated with conventional immunosuppressive therapy experienced one or more relapses. Two relapses were also observed in RTX/IVIgG group.

Eighteen recently diagnosed patients (12.4%) non-responders to conventional therapy are still in treatment with Rituximab.

Conclusion

Future research should be focused on designing sustainable cost first-step biologic protocols to minimize steroid adverse events and produce sustained prolonged remissions.

AUTO1-0610
B AND T CELLS

PRO-RESOLVING LIPID MEDIATORS ARE NOVEL CRTICAL MODULATORS OF T-HELPER CELLS: IMPLICATIONS FOR AUTOIMMUNITY

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Background

Resolution of inflammation is a finely regulated process mediated by specialized pro-resolving lipid mediators (SPMs) that include docosahexaenoic acid (DHA)-derived resolvins and maresins. The role of these molecules in modulating the key cells of autoimmunity is unkown.

Method

Peripheral blood mononuclear cells were obtained from human subjects and from Elovl2-/- mice. The immunophenotype and function of the different T-helper subsets and Tregs were analyzed by polychromatic flow cytometry, qRT-PCR, immunoblotting and ELISA.

Results

Here we show that specific SPMs, resolvin D1 and Maresin 1, reduce TNF-α, IFN- and IL-17 cytokine production from both activated CD8 and CD4 T-cells, without modulating T cell inhibitory receptors or abrogating their capacity to proliferate. Moreover, these SPMs prevented naïve CD4+ T cells differentiation into highly pathogenic T_H1, T_H17 and T_H22 by downregulating their signature transcription factors T-bet, Rorc and AhR as well as promoting *de novo* generation and function of Foxp3+ regulatory T (Treg) cells, without affecting the induction of T_H2 cells. Most of these effects were mediated by GPR32 and ALX/FPR2 receptors and were also confirmed in a mouse model lacking DHA synthesis (Elovl2-/-) and injected with resolvin D1. In addition, we also observed that both resolvin D1 and Maresin 1 promoted Th17 transdifferentiation into Treg cells.

Conclusion

Overall, these findings unveil hitherto unknown actions of specific SPMs on several T-helper cells, providing new mechanisms for SPM-based approaches in modulating chronic inflammatory and autoimmune diseases characterized by imbalances of such pathogenic or regulatory T cell subsets.

AUTO1-0097
B AND T CELLS

CHANGES IN TH17, T EFFECTOR AND TREG SUBPOPULATIONS TREATED WITH ANTI-TNFA THERAPY IN PATIENTS WITH ULCERATIVE COLITIS

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Background

The dynamics between Th17, Teffs (activated T effectors) and Treg subpopulations determine the development of inflammatory process in chronic inflammatory bowel diseases. Recently, data on the effect of anti-TNFα therapy on Th17/Teffs/Tregs subsets have been accumulated, mainly in Crohn's disease. Our aim was to monitor for a period of 1 year Th17/Teffs/Tregs in patients with ulcerative colitis (UC) and anti-TNFa therapy.

Method

Th17, Teffs and Treg in peripheral blood were tested by flowcytometry in patients (before therapy, on week 6, on 3-th month, on first year) and 15 healthy controls. Four patients with anti-TNFa therapy were followed immunologically and clinically.

Results

We found that before therapy the mean percentage of Th17 lymphocytes in patients (8.42%) was lower than in healthy subjects (15.3%). During the therapy the patients increased Th17 level but below the mean percentage found in healthy subjects. Regarding Tregs, their percentage as well was lower before treatment compared to healthy subjects (5.2% vs. 8.9%, respectively). Three patients showed a significant increase in Tregs (mean 11.22%) at the end of the first year, while one patient did not demonstrate such effect. The described changes correlated with the course of the disease. During the therapy there was a decrease in Teffs in three patients with established clinical improvement and a rise of Teffs in one patient without clinical remission.

Conclusion

Our results demonstrated that biological therapy affects Th17, Teffs and Treg subsets and the changes in these subsets could be predictable for the patients about the response to anti-TNFa therapy.

AUTO1-0116
B AND T CELLS

DECREASED EXPRESSION OF SERINE/ARGININE-RICH SPLICING FACTOR 1 IN T CELLS FROM PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS CONTRIBUTES TO REDUCED EXPRESSION OF RASGRP1.

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Background

Serine/arginine-rich splicing factor 1 (SRSF1) binds pre-mRNA to regulate alternative splicing of many genes including T cell receptor associated CD3ζ . Reduced SRSF1 levels are known to be responsible for alternative splicing of CD3ζ in T cells from systemic lupus erythematosus (SLE) patients. RasGRP1 is highly expressed in T cells and activates small GTPase Ras. SLE T cells expressed an alternatively spliced (AS) form of RasGRP1 mRNA lacking exon 11 with reduced RasGRP1 protein levels. The purpose of this study was to determine if SRSF1 controls alternative splicing of RasGRP1.

Method

T cells were collected from 45 SLE patients, 11 RA patients and 18 healthy subjects. Expression levels of SRSF1, wild type (WT) RasGRP1 and the downstream DNA methyltransferase (DNMT) 1 were assessed by quantitative PCR. Direct binding between SRSF1 and RasGRP1-exon11 mRNA was evaluated by oligonucleotide-protein pulldown assay. Human T cells were transiently transfected with SRSF1 specific siRNA to evaluate the effect on RasGRP1 expression.

Results

Expression levels of SRSF1 were significantly lower in SLE patients compared with healthy subjects. In SLE T cells, SRSF1 transcript levels inversely correlated with SLE disease activity, but positively with those of RasGRP1-WT and with DNMT1. SRSF1 directly bound to RasGRP1-exon11 mRNA. Silencing of SRSF1 in human T cells induced increased ratio of RasGRP1-AS to WT and decreased RasGRP1 protein.

Conclusion

SRSF1 controls normal splicing of RasGRP1 and subsequent protein expression, thereby downstream DNMT1 expression. We propose that SRSF1 regulates the splicing of important genes in SLE T cells including RasGRP1 and CD3ζ

AUTO1-0757
B AND T CELLS

HYPOMETHYLATION OF STAT1 AND HLA-DRB1 IN CD8+ T CELLS IS ASSOCIATED WITH TYPE-I INTERFERON-DEPENDENT ACTIVATION OF CD4+ T CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by epigenetic dysregulation, and increased autoantibody and type I interferon (IFN) production. The goal of this study was to explore possible pathogenic roles of CD8+ T cells in SLE through characterizing DNA methylation changes.

Method

Genome-wide DNA methylation of SLE and matched healthy control CD8+ T cells was measured using Infinium Human Methylation 450k arrays. Cell surface expression of HLA-DRB1 on CD8+ T cells with and without IFNα was measured by flow cytometry. Co-incubation of IFNα-treated CD8+ T cells with autologous naïve CD4+ T cells were performed.

Results

SLE CD8+ T cells had 188 hypomethylated CpG sites compared to healthy matched controls. Among the most demethylated were sites associated with *HLA-DRB1* (Db = -0.33) and *STAT1* (Db = -0.15). Treatment with IFNα significantly upregulated HLA-DRB1 on CD8+ T cells of SLE patients but not healthy controls. Co-incubation of naïve CD4+ T cells with IFNα-treated HLA-DRB1+CD8+ T cells led to increased expression of the stimulation marker CD69 on CD4+ T cells in SLE patients, but not in healthy controls. There was a significant increase in STAT1 mRNA levels in both SLE patients and controls with IFNα treatment.

Conclusion

HLA-DRB1 and *STAT1* loci are hypomethylated and epigenetically poised for overexpression in SLE CD8+ T cells in the presence of type-I interferon. IFNα-treated lupus CD8+ T cells stimulate autologous CD4+ T cells *in vitro*. These data suggest a pathogenic role for CD8+ T cells in a high type-I interferon environment in SLE patients.

AUTO1-0280
B AND T CELLS

GITRL/GITR PROMOTES FOLLICULAR HELPER T CELLS IN AUTOIMMUNE ARTHRITIS

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Background

Glucocorticoid-induced TNFR-related protein (GITR) belongs to the tumor necrosis factor receptor superfamily (TNFRSF). In recent years, numerous studies have indicated that GITR and its ligand (GITRL) are involved in regulating the development and function of immune cells in both the innate and adaptive immune systems, but the role of GITRL/GITR signaling in modulating CD4+ follicular helper T (Tfh) cell response during autoimmune arthritis remains largely unclear.

Method

The expression of GITR on Tfh cells from the spleen of CIA mice was analyzed, and Tfh cells were stimulated by GITRL *in vitro*. To examine the effect of blocking GITRL-mediated signaling, GITR-Fc protein was adminstrated w in CIA mice.

Results

We showed that splenic Tfh cells from collagen-induced arthritis (CIA) mice expressed higher levels of GITR compared with non-Tfh cells. In vitro, GITRL treatment markedly enhanced the percentage and number of Tfh cells. The administration of GITR-Fc in CIA mice suppressed the Tfh cell response, resulting in a reduced production of autoantibodies and the number of autoantibody-secreting cells in both the spleen and bone marrow.

Conclusion

Together, these results indicate that blockade of the GITR pathway can ameliorate arthritis progression by mainly modulating the Tfh cell response.

AUTO1-0245
B AND T CELLS

DISSECTING THE CD8 T CELL REACTIVITY IN NARCOLEPSY

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Background

Narcolepsy type 1 is a sleep disorder caused by the loss of signaling through the sleep-regulating neuropeptide hypocretin. It is thought to be the result of an autoimmune attack on the hypocretin producing neurons, though direct evidence is still lacking. Several factors point to the immune system as an important player in disease development, most importantly the strong correlation between Narcolepsy and the HLA class II allele HLA-DQB1*06:02, expressed by >98% of patients, and the drastic increase in Narcolepsy incidence following the 2009/2010 vaccination against H1N1 influenza virus. We aim to dissect the reactivity of CD8 T-cells from Narcolepsy patients in order to get an insight into what potentially causes the immune system to attack hypocretin producing neurons.

Method

Using the NetMHC prediction server we have predicted 914 epitopes from 6 hypocretin neuron-specific proteins spanning 8 different HLA class I alleles. PBMC samples from 33 Narcolepsy patients and 69 controls are screened for the presence of CD8 T-cells reactive towards any of these 914 peptides utilizing a novel technology for high-throughput detection of specific T cells. In this method 914 unique peptide/MHC complexes are generated and coupled to a dextramer backbone holding both a fluorochrome and an individual DNA barcode. The specific CD8 T-cells are then sorted based on the fluororescence signal and through deep sequencing the individual DNA barcodes are identified, revealing the peptide specificity of the CD8 T-cells.

Results

The study is ongoing, but we have detected specific T-cells in a cohort of the patients and controls.

Conclusion

No conclusions yet.

AUTO1-0454
B AND T REGULATORY CELLS

TNFR2+ REGULATORY T CELLS SUBPOPULATIONS ARE HIGHLY SUPPRESSIVE AND ARE INCREASED ON ANTI-TNF TREATMENT IN RHEAUMTOID ARTHRTIS PATIENTS.

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Background

In rheumatoid arthritis (RA), regulatory T cells (Tregs) fail to control chronic inflammation. TNF-α is involved in inhibition of Tregs differentiation and activation but the respective roles of its two receptors is unclear.

We aimed to establish the role of TNFR2 on Tregs in control of inflammation by studying: 1) the action of TNF on Treg function in the presence and absence of TNFR2 in vitro and 2) in a model of skin inflammation in TNFR2KO mice, 3) the evolution of TNFR2-expressing Tregs from RA patients during anti-TNF-treatment.

Method

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Results

In vitro, TNF-α enhanced Foxp3 maintenance through TNFR2 signaling in cultured Tregs. In vivo, TNFR2-negative-Treg cells from both TNFR2KO and CRE-FoxP3-TNFR2 lox/lox mice (in which only Tregs are deficient for TNFR2), had lower spontaneous suppressive capacities (lower inhibition of effector T cell proliferation and IFN-g production). FoxP3 methylation (analysed by bisulfate conversion) was higher in Tregs from TNFR2KO mice than *wt* mice. This suggested that TNFR2 expression confers higher stability to Tregs.

TNFR2KO mice had enhanced imiquimod induced skin-inflammation and decreased Tregs and $CD39^+$ Tregs frequencies in lymph nodes. In RA patients (n= 15) responding to anti-TNF treatment, an increase in TNFR2-expressing-Tregs frequencies was evident at 3 months of treatment vs. the baseline. Conversely, no variation was observed in patients with axial spondylaorthritis patients (n=19)

Conclusion

TNFR2 signaling on Tregs may play a major role in controlling inflammation and can be activated both by TNF-α and anti-TNF treatment. Further studies to dissect TNFR2 dependent pathways on Tregs are warranted.

AUTO1-0727
B AND T REGULATORY CELLS

LYMPHOPENIA-ASSOCIATED UNSTABLE T-CELL REGULATION MIRRORS DISEASE ACTIVITY-RELATED CLONAL T-CELL EXPANSIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background

Related to associated deficiencies of IL-2 and surface CD25 (IL2R-alpha), Foxp3+ T-regulatory cells (Tregs) are dysfunctional in SLE. We have previously shown that this defect can be specifically quantified by the drastic reduction of the otherwise strong CD25 upregulation that Tregs undergo upon activation.

Method

We tracked CD4+ T-cells longitudinally in 33 SLE patients cytometrically and clonally by TCR-beta sequencing.

Results

We uncovered surprisingly wide fluctuations of activated Treg frequencies over time, with individual amplitudes strongly correlated to SLEDAI disease activity, plasma IgG anti-dsDNA and lymphopenia. Resembling coupled Treg and conventional T-helper cell oscillations, these frequency fluctuations were compatible with an unstable regulation circuit modeled by a classic Lotka-Volterra-type predator-prey model, which fitted frequency data of 15/19 patients with >3 followups with realistic dynamic turnover and suppression rates. Strikingly, individual model-derived Treg suppressivity was strongly correlated with the independently measured CD25 upregulation (see above) and with blood lymphocyte levels. Thus we hypothesized that this T-cell regulatory instability, reflected by the dynamics of functionally related lymphopenia, could mirror the de-suppression of pathogenic T-cell clones. Frequencies of highly expanded clones in each patient indeed co-varied significantly with lymphopenia over time, expanding when blood lymphocytes were low. Clones with such negative lymphocyte correlations were furthermore likely pathology-related since (a) significantly enriched in patients with higher disease activity, and (b) more positively related to individual SLEDAI changes over time than other traceable clones.

Conclusion

We conclude that lymphopenia-related destabilized T-cell regulation could be responsible for relative expansions of pathogenic T-cells in SLE, possibly resulting in disease flares.

AUTO1-0188
B AND T REGULATORY CELLS

DESENSITIZATION USING SELF-ANTIGEN DS-DNA INHIBITS B AND T CELL FUNCTIONS BY MODULATING T-REG CELL AS REGULATOR IMMUNE SYSTEM IN LUPUS MICE MODEL

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Background

The aim of this study was to develop a novel therapeutic method for improving immune system regulation in SLE using self-antigen dsDNA.

Method

A total of 25 female BALB/c mice were divided into 2 groups: 20 mice received a single intraperioneal injection of 0.5 mL pristane for lupus induction and 5 mice as healthy controls. Starting at 8 weeks after injection, 15 pristane-induced lupus mice were divided into three groups according to the dosis that were received : 0,005 µg, 0,05 µg, and 0,5 µg of self dsDNA desensitization. The doses would be increased ten times every week. Self dsDNA were complexed with the cationic polyethylenamine before injection. Four week after desensitization 25 mice were sacrified and analyzed for serum autoantibodies levels (dsDNA antibody, ANA) and TGF-β using ELISA and T-reg, dendritic cell maturation from spleen using flow-cytometry.

Results

Escalating dose antigen spesific therapy with dsDNA decreased ANA levels (21.6 vs 30.4 p=0.02) significantly compare to positive control, decreased anti-dsDNA (20.7 vs 68.3 p=0.08), decreased dendritic cell maturation (1.96 vs 2.94 p=0.84) and decreases Th17 cells (3.62 vs 5.62 p=0.18). Desensitization using self-antigen dsDNA was increased T-reg proliferation (10.57 vs 18.38 p=0.019) and level of TGF-β (732 vs 261.02 p=0.03) significantly compare to control positive

Conclusion

In conclusion, desensitization using self-antigen dsDNA was able to modulate T-reg as a regulator immune respon and inhibit B and T cell functions in lupus mice model.

AUTO1-0190
B AND T REGULATORY CELLS

CORRECTION OF INFECTION-INDUCED INFLAMMATION IN PRIMARY IMMUNODEFICIENCY BY ADOPTIVE TRANSFER OF REGULATORY T CELLS

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Background

Adoptive transfer of regulatory T cells (Tregs) have been used to treated autoimmune diseases, GvHD and transplantation rejection. In the present study, we explored the therapeutic potential of Tregs to treat inflammation accompanied with primary immunodeficiency. We and others have previously demonstrated that *Xiap*-deficient mice are highly susceptible to infection by selective pathogens such as *C. albicans*, with resulting syndromes analogous to X-linked lymphoproliferative syndrome type-2 (XLP-2), a primary immunodeficiency disease. Low-dose *C. albicans* infection killed *Xiap*$^{-/-}$ mice by inflammation, but does not affect the viability of WT C57BL/6 mice.

Method

To determine whether transfer of wild-type (WT) Tregs reversed infection-induced inflammation of *Xiap*$^{-/-}$ mice, WT Tregs were administered into *Xiap*$^{-/-}$ mice after *C. albicans* infection.

Results

Administration of WT Tregs 2 days after *C. albicans* infection partly rescued the survival of *Xiap*$^{-/-}$ mice; 60% of infected *Xiap*$^{-/-}$ mice that received WT iTregs survived 40 days after infection, whereas all untreated *Xiap*$^{-/-}$ mice had died by 18 day post-infection. WT Tregs transfer also alleviated kidney inflammation and suppressed the high levels of serum inflammatory cytokines in untreated infected *Xiap*$^{-/-}$ mice. Moreover, the delivery of WT Tregs effectively reduced fungal burden in infected *Xiap*$^{-/-}$ mice. Notably, the transfer of WT Tregs did not interfere with the generation of *C. albicans*-specific T helper 17 cells.

Conclusion

These results suggest that XIAP-intact Tregs restore the ability of *Xiap*$^{-/-}$ mice to respond to infection and infection-induced inflammation. Furthermore, our study suggests that Tregs could be used to treat primary immunodeficiency.

AUTO1-0309
B AND T REGULATORY CELLS

GENE-/ENVIRONMENT INTERACTIONS IN THE DEVELOPMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS. A REVIEW AND POWER STUDY - GETTING THE SIZE RIGHT.

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Background

SLE very likely results from an interaction where environmental factors trigger the development of SLE in genetically susceptible individuals; however, no strong associations have been established. We aim to review the role of gene-/environmental interactions on the risk of SLE. Furthermore, we address aspects of statistical power for future studies which also include gene-environment interaction.

Method

Review is based on literature search on Medline using the search term: '*gene-environment interaction AND systemic lupus erythematosus.'* Comprehensive sample size requirements are exemplified in the following setting: Estimated risk ratios for SLE of 1.5 for current smoking (prevalence of 22%) as well as carriage of polymorphisms in the *signal transducer and activator of transcription* (prevalence of 30%); interaction effect=2; alpha=0.05. Power-sample size relations were calculated using an iterative statistical approach.

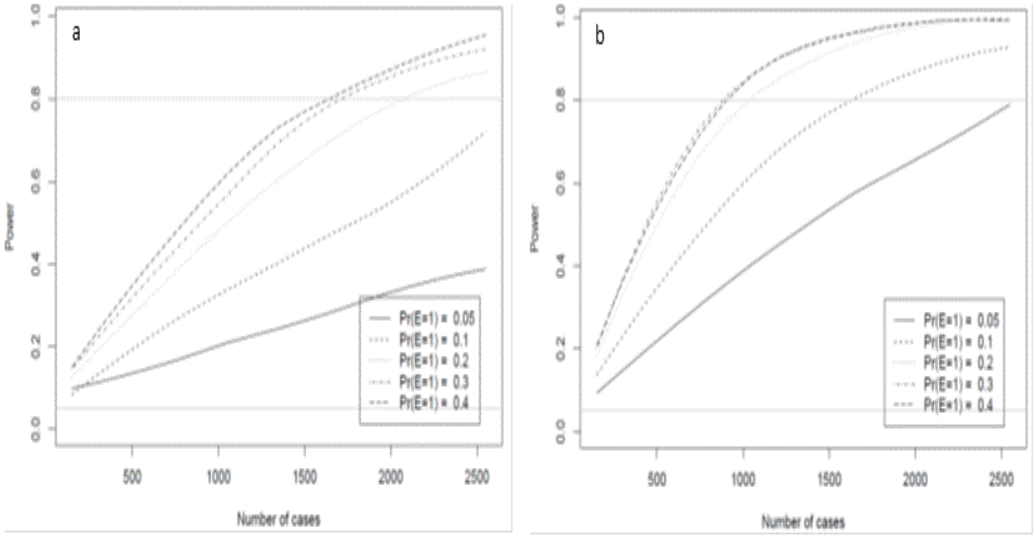
Results

We identified 3/40 publications containing original data on gene-environment interaction. Further four studies were identified by examining the reference lists of all articles. These studies were focused on prevalent genes coding various xenobiotic enzymes potentially interacting with smoking, sun exposure and exposure to hazardous waste.
The studies identified were of small size and not powered to study polymorphisms of lower prevalence. We find that inclusion of controls in a 1:10 ratio may compensate for

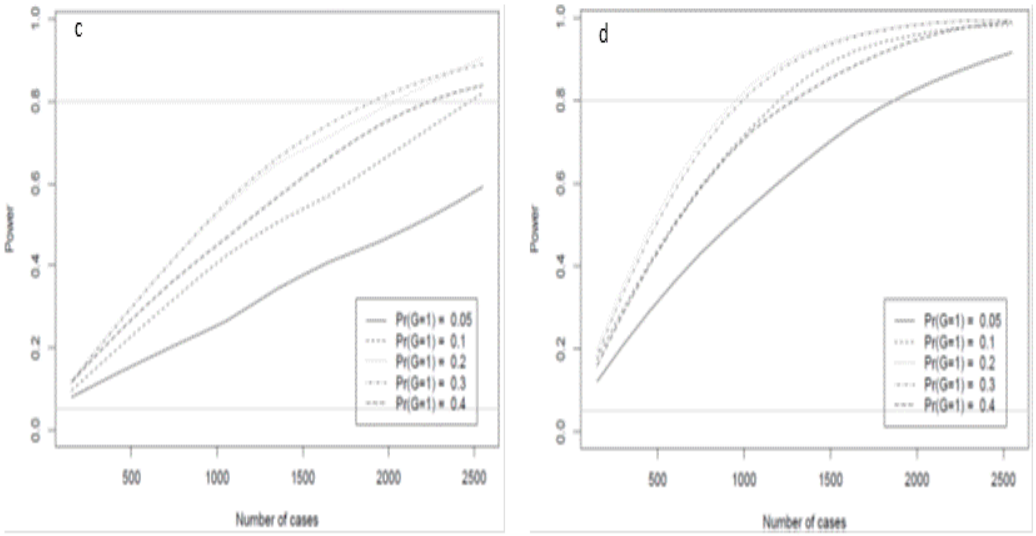
about half of the needed case sample, Figure.

Figure 1. Number of cases required to detect a Gene-Environment Interaction of magnitude $R_{ge} = 2$. Relative risk of SLE for both genetic- and environmental factor = 1.5, significance level = 0.05, 2-sided alternative.

a+b: Pr(G=1)* = 0.3 (*STAT4*-variant). Case:control-ratios are 1:1 and 1:10, respectively.



c+d: Pr(E=1)** = 0.22 (daily smokers^). Case:control-ratios are 1:1 and 1:10, respectively.



*Pr(G=1) = Prevalence of risk gene, homo- or heterozygote, dominant inheritance assumed.

**Pr(E=1) = Prevalence of environmental exposure.

^ The Danish Health Authority, published in 2013.

Conclusion

Only few studies have focused on gene-environment interactions in SLE and none have included immune-related gene polymorphism of central significance to SLE pathogenesis. Such studies are in wanting and need to be of sufficient power regarding single effects as well as interaction.

AUTO1-0164
B AND T REGULATORY CELLS

AGE-ASSOCIATED B CELLS WITH PROINFLAMMATORY CHARACTERISTICS ARE EXPANDED IN A PROPORTION OF MULTIPLE SCLEROSIS PATIENTS

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Background

Immune aging occurs in the elderly and in a proportion of multiple sclerosis (MS) patients. Recently, $IgD^{-}CD27^{-}$ double negative (DN) and $CD21^{-}CD11c^{+}$ ($CD21^{low}$) B cells were described as age-associated B cells. This study aimed to investigate the prevalence and functional characteristics of age-associated B cells in MS patients.

Method

Using flow cytometry, age-associated B cell frequencies were measured in the peripheral blood of 64 MS patients and 85 healthy controls (HC) and in paired peripheral blood and cerebrospinal fluid (CSF) of 6 MS patients. Expression of costimulatory (CD80, CD86) and MHC-II molecules was determined on DN B cells of 47 MS patients and 31 HC. DN B cell cytokine production was analyzed for 13 MS patients and 11 HC following *ex vivo* stimulation.

Results

A higher proportion of MS patients younger than 60 years with peripheral expansions of DN (20%) and $CD21^{low}$ (22%) B cells was demonstrated compared to age-matched HC (3% and 6%, respectively). DN and $CD21^{low}$ B cell frequencies were even further increased in the CSF. DN B cells showed similar (MS patients) or increased (HC) MHC-II expression as class-switched memory B cells and intermediate costimulatory molecule expression between naïve and class-switched memory B cells. Further, DN B cells produced proinflammatory and cytotoxic cytokines.

Conclusion

In conclusion, a proportion of MS patients showed increased peripheral expansions of age-associated B cells. DN and $CD21^{low}$ B cell frequencies were further increased in MS CSF. These cells could contribute to inflammation by induction of T cell responses and the production of proinflammatory cytokines.

AUTO1-0798
B AND T REGULATORY CELLS

CD72: A REGULATORY MOLECULE OF B CELLS IN SLE PATIENTS.

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Background

The role of B cells in SLE is central in the development of autoimmunity. They are antigen presenting cells and the source of immunoglobulins. Auto-reactive B cells produce autoantibodies as well as many pro-inflammatory cytokines. B regulatory cells exist in peripheral blood as a small group of cells, but are very important in preventing autoimmunity and maintaining self-tolerance. The many faces of B regulatory cells are characterized by different membrane bound molecules as well as secreted ones. Of special importance is the regulatory molecule CD72, expressed on B cells and reported to have a regulatory role in SLE.

Method

CD72 was evaluated on B cells and sera taken from SLE patients and normal controls. The expression of CD72 on B cells was then assessed in correlation with clinical and laboratory data.

Results

When assessed on B cells taken from SLE patients it was found to be down regulated in association with SLE disease activity, anti-dsDNA and anti-cardiolipin antibodies. In another study, we found elevated serum levels of soluble CD72 in SLE patients when compared to normal controls. Here also, elevated levels were found to be in correlation with disease activity, kidney involvement and increased titers of several autoantibodies. Finally, we could demonstrate that CD72 expression was up regulated when SLE patients' B cells were incubated with recombinant human semaphorin3A, another regulatory molecule.

Conclusion

Further studies are needed to better evaluate the mechanisms by which CD72 expression is controlled and how targeting CD72 may become a potential treatment in SLE

AUTO1-0582
B AND T REGULATORY CELLS

NOVEL MICRO-RNA ANTAGONIST COCKTAIL SUPPRESSES THE INFLAMMATION INDUCED BY EXTRACELLULAR VESICLE-MEDIATED TOLL-LIKE RECEPTOR SIGNALING IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Toll-like receptor (TLR) expression and innate immune system activation have a distinct association with systemic lupus erythematosus (SLE). We have shown that TLR7 and TLR8 are up-regulated in PBMCs of SLE patients. Since micro-RNAs (miRs) packaged and secreted in extracellular vesicles (EVs) can bind to TLR7 and TLR8, our objective was to examine the therapeutic application of miR antagonists to suppress TLR7/8 inflammatory signaling in SLE.

Method

Cells were treated with miR antagonists and/or EVs in vitro. PBMCs were isolated from active SLE patients and adoptively transferred into immunodeficient NOD-scid IL-2rγ (null) mice to produce chimeras containing PBMCs from SLE patients.

Results

EV-encapsulated miRs induced TLR8 expression and cytokine secretion in PBMCs from SLE patients and healthy controls; up-regulation of these factors was significantly reduced with the addition of MyD88 inhibitor or chloroquine. Similarly, locked nucleic acid (LNA) miR antagonists also reduced TLR8 activation. Chimeric SLE mice transfected with an LNA miR inhibitor cocktail (MIC) suppressed the robust infiltrates in the small intestine, liver, and kidney in control mice. Immunohistochemical staining of these infiltrates confirmed human CD3+ T-cell presence. Despite human T-cells, B-cells, monocytes, and NK cell detection from whole blood of chimeric mice at similar levels, levels of human IL-2, IL-6, IL-10, and TNF-α were reduced with MIC.

Conclusion

These results establish a novel model of SLE to further explore the therapeutic efficacy of antagonizing EV-encapsulated miRs to suppress innate immunity in SLE. Ongoing studies include exploring specific antagonist combinations and RNA-sequencing of EV-derived miRs to define therapeutic targets and biomarkers.

AUTO1-0954
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

GENETIC PROFILE IN BEHÇET'S DISEASE PATIENTS WITH AND WITHOUT OCULAR MANIFESTATIONS TO ANALYZE THE HLA POLIMORPHISM IN BEHÇET'S DISEASE PATIENTS WITH AND WITHOUT OPHTHALMOLOGICAL MANIFESTATION

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Background

Behçet's disease (BD) has a non-uniform geografical distribution, association with HLA B*51, and ophthalmologic manifestation is the most frequent after oral ulcer. OBJECTIVE: To evaluate the frequency of HLA class I and II alleles in patients with BD with and without ophthalmological manifestation and healthy controls.

Method

Cross-sectional study with a control group.BD patients from the rheumatology to ophthalmology department of UERJ, together with UNIFESP. Criteria for inclusion: > 18 years of age,International Study Group on Behçet's Disease . Inclusion criteria for controls: > 18 yaers of age and absence of autoimmune diseases. Epidemiological and clinical data were documented in rheumathology. The ophthalmologic data examination was based on the presentation form and the intensity of the ocular inflammation by the Standardization Uveitis Nomenclature Working Group and fluoescein retinoangiography images. Class I and II HLA genotyping was by the PCR-SSP method. It has the funding of the Rheumatology 's Society of Rio de Janeiro and approval in the CEP of both Universities

Results

The results, so far, have shown that the C*02 locus is significantly more frequent in the DB with systemic manifestation than the controls, B*27 had a higher prevalence in the group with BD and ocular manifestation than controls and DRB1*04 appears to be protective of DB.

Conclusion

HLA plays a major role in various aspects of Behçet's disease. However, it is not useful for diagnosis, but as a marker of disease risk which may influence the conduct as the closest follow up of the patient and an intervention more being aggressive.

AUTO1-1039
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

BIOPSY UTILITY IN THE WORKUP OF ANCA-ASSOCIATED VASCULITIS – A CASE REPORT AND LITERATURE REVIEW

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Background

In ANCA - associated vasculitides (AAV), a positive biopsy is supportive of vasculitis diagnosis, however account must be taken of its limitations and contraindications.

Method

79 years old, Caucasian women, history of Sjögren Syndrome, Sarcoidosis, hypotiroidism and Parkinson's disease. Admitted with symptomatic anaemia, no bleeding or fever. Lab: microcytic hypochromic anaemia (Hb 7,7g/dL), ESR 91mm, PCR 4,5mg/dL, ferritin 84,9ug/L, creatinin 1,4mg/dL; urinalysis: red blood cells >1800/uL, proteinuria (24h) 1271mg/dL. In a further workup ANCA antibodies were detected (MPO 196,8UQ, negative PR3), positive ANA antibodies (1/1280), negative DS-DNA AB. Body CT Scan: small pleural effusion, ground-glass appearance (all pulmonary parenchyma). BAL: abundant hemosiderophages. Pulmonary biopsy: parenchymal focal vascular congestion. Remission induction therapy: corticoids, cyclophosphamide pulses. Azathioprine was initiated as maintenance therapy, with concomitant lower corticoid doses. In 6 months follow – up period the patients presented a lower MPO value (51.1 UQ), ESR (53mm) and a stabilization of kidney function, with no red blood cells or proteins in urinalysis.

Results

We discuss a pulmonary – renal syndrome with a probable ANCA –associated vasculitis, with a negative pulmonary biopsy for vasculitis. No renal biopsy was performed based in risk/benefit issues.

Conclusion

A positive MPO – ANCA in a patient with suspected nephritis has >95% association with necrotizing crescentic glomerulonephritis therefor, in particular cases, biopsy could be dismissed. For a suspected AAV, biopsy could be indicated when MPO – ANCA assays are negative, borderline or in further evaluation of relapsing vasculitis.

AUTO1-0920
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

PAIN IN RHEUMATOID ARTHRITIS: DID THE USE OF BIOLOGIC AGENTS MODIFY PAIN PERCEPTION ?

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Background

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterised by inflammation of the joints. Patients with RA often experience diminished health-related quality of life (HRQOL) with respect to both physical functioning and emotional state due to the pain, fatigue and disability that can result from this inflammation. Patients report that, from their perspective, these measures of HRQOL are more important than traditional measures of clinical disease activity. Our aim was to underline the effects of cDMARDs and bDMARDs on chronic pain in RA.

Method

English-language articles published between January 1995 and July 2017 were found in the PubMed, Medline, and Cochrane Library databases using the key words “rheumatoid arthritis” or “inflammatory arthritis”, “arthritis” and “pain” or "chronic pain" or widespread chronic pain". The articles and book chapters in the papers’ reference lists were also reviewed.

Results

Pain processing by the central nervous system can maintain and augment RA pain, and is a promising target for future treatments. Clinical studies have reported associations between inflammatory disease activity, as measured by DAS28, and pain sensitisation. Pain sensitisation might inflate DAS28 values even in the absence of ongoing synovitis. The RCTs that evaluated current DMARD usage (especially methotrexate) showed reductions in pain that were both statistically and clinically significant. However, participants still reported pain at final follow up

Conclusion

Given the number of the biologic treatment options for the RA population, clinicians are faced with a challenging choice regarding the optimal treatment. There is no RCT that evaluates all approved biologics to answer this question.

AUTO1-0187
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

ASSOCIATION BETWEEN ALLELIC VARIANTS OF THE HUMAN GLUCOCORTICOID RECEPTOR GENE AND AUTOIMMUNE DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background

The human glucocorticoid receptor gene (*NR3C1*) is considered to play a role in the differences and sensitivities of the glucocorticoid response in individuals with autoimmune diseases. The objective of this study was to examine by means of a systematic review previous findings regarding allelic variants of *NR3C1* in relation to the risk of developing systemic autoimmune diseases.

Method

Studies that analysed the genotype distribution of *NR3C1* allelic variants among patients with systemic autoimmune diseases were retrieved. A meta-analysis was conducted with a random effects model. Odds ratios (ORs) and their confidence intervals (CIs) were calculated. In addition, sub-analysis by ethnicity, sensitivity analysis and tests for heterogeneity of the results were performed.

Results

Eleven studies met the inclusion criteria for meta-analysis. We found no evidence that the analysed *NR3C1* polymorphisms, rs6198, rs56149945, and rs6189/rs6190, modulate the risk of developing a systemic autoimmune disease. Nonetheless, a protective role for the minor allele of rs41423247 was found among Caucasians (OR = 0.78; 95% CI: 0.65, 0.92; *P* = 0.004). A subgroup analysis according to underlying diseases revealed no significant association either for Behçet's disease or rheumatoid arthritis, while correlations between *NR3C1* polymorphisms and disease activity or response to glucocorticoids could not be evaluated due to insufficient data.

Conclusion

There is no clear evidence that the analysed *NR3C1* allelic variants confer a risk for developing systemic autoimmune diseases although the minor G allele of rs41423247 may be protective among Caucasians.

AUTO1-0173
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

RATIONAL USE OF METHYLPREDNISOLONE FOR TREATMENT OF IMMUNE MEDIATED DISEASES: RELATIONSHIP BETWEEN DOSING, EFFECTIVENESS AND SAFETY

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Background

Methylprednisolone (MP) has high anti-inflammatory potency, but the precise doses and its benefit/risk balance are still not clear. Our objective was to assess the pattern of use of MP pulses in clinical practice.

Method

Retrospective descriptive study of all the patients who received MP pulses for autoimmune mediated disease treatment in three Uruguayan hospitals from 2013 to 2015. Age, gender, immune mediated disease, comorbidities, concomitant treatment, MP dosing, clinical response and adverse reactions were analyzed.

Results

164 cases were included. Mean age was 48.4 (SD: 18); 118 (72%) were female. The average dose of MP was 3.35 g (SD 1.4) and it was administrated in a mean of 4 days (SD: 1.56). 92 (56.1%) had immune mediated neurologic disease, 72 (44%) other immune mediated diseases. Complete response occurred in 77 (47%), partial response in 62 (37.8%) and non- response in 25 (15.2%). 42 (25.6%) presented adverse reactions, only 6 were severe. Fifteen (68%) patients treated with MP pulses ≤ 1.5 g, 38 (43.7%) who received pulses between 1.5-3 g and 24 (43%) treated with pulses > 3 g had complete responses ($p > 0.05$). Adverse reactions were reported in 14 (25%) cases who received >3 g, 21 (24%) who received pulses of 1.5-3 g and 7 (32%) with pulses of < 1.5 g. ($p > 0.05$)

Conclusion

No relationship was found between MP pulse dose and clinical response or safety concerns in immune mediated diseases. Prospective studies should be performed to add evidence about this issue.

AUTO1-0976
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

CLINICAL IMPLICATIONS AND PATHOLOGICAL CLASSIFICATION OF TUBULOINTERSTITIAL INJURY FOR THE PREDICTION OF RENAL OUTCOME IN LUPUS NEPHRITIS

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Background

Lupus nephritis is the first clinical manifestation in 15 to 20% of the patients and up to 60% of the patients will develop clinically relevant nephritis at some point in the course of the disease. Tubulointerstitial lesions are a common finding and impact in renal outcome independently of glomerular lesions. However, the current classification does not include a mandatory score of this kind of injury.

Method

The authors aim to determine predictors and influence of tubulointerstitial involvement in renal outcomes and treatment response in a cohort of 82 patients with 100 biopsy-proven Lupus nephritis flares diagnosed and treated in the Hospital Clinic (Barcelona) between 2006 and 2016.

Results

Tubulointerstitial chronic damage and inflammation were present in 74% of the biopsies. Patients with inflammation grade ≥ 1 (>25%) had worse renal function and higher proteinuria than patients with no inflammation. More fibrosis correlated with worst renal function, especially in those with fibrosis grade 3 (> 50%). Fibrosis >25% was an independent predictor of renal survival and increased the possibility of renal failure stage 4 KDOQI and progressive glomerular filtration rate decline. Acute inflammation correlated with the presence of acute kidney injury and hematuria with casts at presentation. Around 40% of patients in clinical remission still had significant inflammation in control biopsy.

Conclusion

Tubulointerstitial chronic damage and inflammation have an important impact in renal outcomes and are essential in treatment response assessment. Additionally, a proper evaluation of urine sediment is an important tool to detect early tubulointerstitial lesions in Lupus nephritis.

AUTO1-0690
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

PET/MR IN LARGE-VESSEL VASCULITIS: CLINICAL VALUE FOR THE DIAGNOSIS AND ASSESSMENT OF DISEASE ACTIVITY

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Background

The diagnosis and the activity determination could be challenging in large-vessel vasculitis (LVV). The aim of this study was to analyze the value of hybrid PET/MR in LVV.

Method

All consecutive patients with LVV who underwent PET/MR were included. PET/MR patterns were defined as inflammatory in the case of positive PET (grade=3) and abnormal MR (stenosis and/or wall thickening) and fibrous in the case of negative PET (grade 1 or 2) and abnormal MR.

Results

Thirteen patients with median age at 67 years (23-87 years) and 10 (77%) females were included, and underwent 18 PET/MR scans. Eleven PET/MR performed at diagnosis (n=4) or relapse (n=7) and 7 in patients in remission. 8/18 (44%) had PET/MR inflammatory pattern and 3/18 (17%) had fibrous pattern. PET/MR were normal in 2/10 (20%) cases of TA versus 5/8 (62%) cases of GCA (p=0.3). The median SUVmax was 3.0 [1.8- 8.6] without significative difference between GCA and TA: 3.4 (2.1 – 8.6) versus 2.6 (1.8- 7.1) (p=0.4), respectively. Eleven PET (61%) were performed under treatment, which consisted of steroids with a median dose at 30 mg/day [3-240]. Among 11 patients with active disease, 8 had inflammatory patterns and 3 had normal PET/MR, i.e a sensibility of 73%, and the sensibility increased to 100% in patients with active TA disease. Median SUVmax were 4.7 [2.1-8.6] in patients with active disease versus 2 [1.8-2.6] in patients with remission (p=0.003).

Conclusion

PET/MR is a new hybrid modality of imaging which is interesting for the diagnosis and the follow-up of large-vessel vasculitis.

AUTO1-0182
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

ECONOMIC IMPACT ANALYSIS OF THE USE OF AN ANTI-DFS70 ANTIBODY TEST IN PATIENTS WITH FEATURES OF UNDIFFERENTIATED SYSTEMIC AUTOIMMUNE DISEASE

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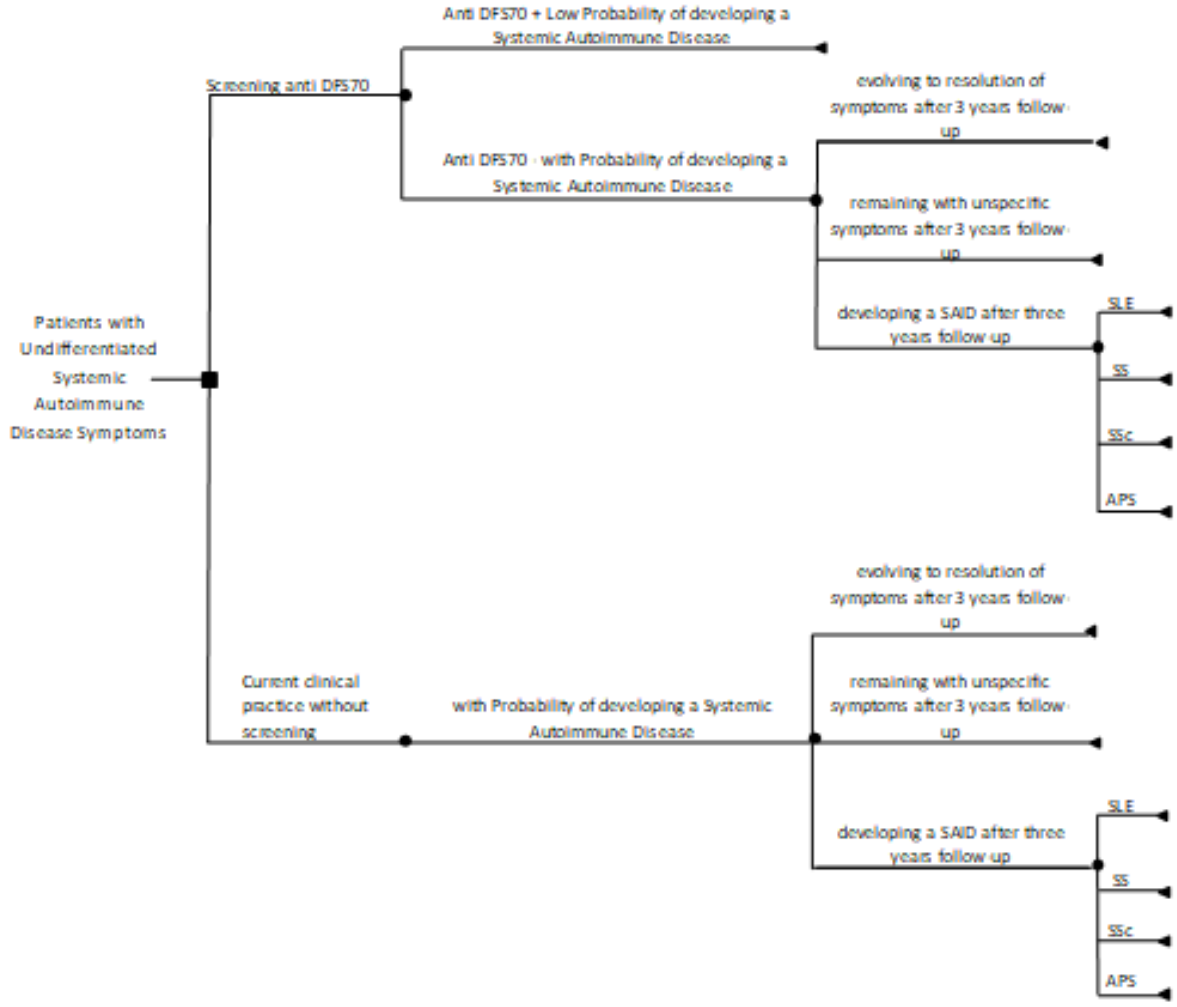
Background

Anti-dense fine speckled-70 (anti-DFS70) antibody represents a new antinuclear antibody (ANA) specificity. They are considered to be more prevalent in healthy individuals. Moreover, in patients with ANA and features of undifferentiated systemic autoimmune disease (SAID) the coexistence of anti-DFS70 was associated with a lower risk to develop a defined SAID. Therefore, they might help in correctly classifying ANA positive patients with undifferentiated SAID and avoiding the use of unnecessary additional diagnostic resources. The objective of this study was to analyze the economic impact of the introduction of the anti-DFS70 antibody test in a hospital setting.

Method

A case-control study was performed to detect anti-DFS70 antibodies in ANA positive subjects without SAID (cases; n=124) and with SAID (controls, n=290). A decision tree was developed to represent the disease course of patients with undifferentiated SAID symptoms in the following three yars. Percentage of patients with positive anti-DFS70 was the main effectiveness variable used. Health resources and unit costs were obtained from Hospital databases/expert consensus. Two analyses were developed: mean cost per patient and budget impact of test implementation.



Results

Among the cases, 5 (4.0%) patients tested positive for anti-DFS70 antibody (positive value ≥20 CU). The mean cost per patient under the current clinical practice (without anti-DFS70 antibody test) decreased from 3,274€ to 3,195€ in our scenario (including anti-DFS70 antibody test). The budget impact reports cost savings of 10,288€.

Conclusion

The introduction of the anti-DFS70 antibody test would avoid unnecessary follow-up and minimize the use of health resources generated by a potential SAID suspicion.

AUTO1-1038
BARCELONA CLÍNIC AUTOIMMUNITY – ALUMNI

ANALYSIS OF 20 YEARS OF SYSTEMIC LUPUS ERYTHEMATOSUS HOSPITALIZATIONS (1995-2015): EVOLUTION THROUGHOUT THE YEARS AND PREDICTORS OF OUTCOME

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Background

Although extensively portrayed in the outpatient setting, characterization of Systemic Lupus Erythematosus (SLE) in the hospitalization setting is still relevant, particularly in the perspective of its evolution over the years.

Method

The authors performed a retrospective analysis of SLE patients hospitalized in the Autoimmune Diseases Department of a university hospital during a 20-year period (1995-2015), describing admission causes, flare characteristics and predictors of outcome.

Results

A total of 814 hospitalizations concerning 326 patients were analyzed. The main causes of admission were flare (40.2%), infection (19.2%) diagnostic procedures (18.8%) and musculoskeletal disorders (3.9%). In patients with active disease, associated antiphospholipid syndrome (APS) (p=0.007, OR 6.601) and thrombocytopenia (p=0.033, OR 4.313) correlated with ICU admission. A mean of 2.46 hospitalizations per patient was observed, with readmission at 30 days occurring in 7.9%, mainly for flare (40.6%). Thrombocytopenia (p=0.005, OR 3.554) and renal involvement (p=0.021, OR 2.521) were associated with readmission. A total of eight patients died during hospitalization: associated APS (p=0.002, OR 26.057) and thrombocytopenia (p=0.035, OR 2.759) correlated with mortality. There was no significant variation in the patients´ demographics (gender, age, SLEDAI and SLICC) across the twenty-year span, while a decrease in arterial thrombotic events and musculoskeletal causes of admission was noted. Regarding therapy, a reduction in the administration of cyclophosphamide and a significant growth in the use of mycophenolate mofetil were detected in recent years.

Conclusion

In the studied sample, the characteristics of SLE hospitalizations have not markedly changed over the past 20 years. Thrombocytopenia featured consistently as a predictor of poor outcome.

AUTO1-0003
BIOSIMILAR AND ALTERNATIVES

LIPOSOMAL DELIVERED ANTIGEN-SPECIFIC TOLERISING IMMUNOTHERAPY TARGETING AUTOREACTIVE CD8+ T CELLS IN NOD MICE

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Background

Type 1 diabetes (T1D) results from autoimmune destruction of insulin-producing pancreatic β cells, involving $CD4^+$ and $CD8^+$ T cells. Non-obese diabetic (NOD) mice are a model for human T1D. As islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) is a major diabetogenic antigen in NOD mice, we developed a model to test IGRP antigen-specific immunotherapy. We showed previously that liposomes co-encapsulating antigen and NF-kB inhibitor induced antigen-specific suppression of $CD4^+$ T cells in mice. These liposomes passively target and deliver their payload to dendritic cells in lymphoid organs, suppressing NF-kB activation.

Method

For the current model, we injected NOD mice with liposomes co-delivering $IGRP_{206-214}$ peptide and NF-kB inhibitor. Twenty four hours after liposome injection to naïve mice, we observed uptake of liposomes specifically by antigen presenting cells (APCs). Delivered peptide was presented by these APCs as CTV-labelled IGRP-specific $CD8^+$ T cells proliferated in draining lymph nodes after subcutaneous delivery of liposomes co-encapsulating $IGRP_{206-214}$ and the NF-kB inhibitor calcitriol. After adoptive transfer of IGRP-specific $CD8^+$ T cells, we enumerated both adoptively-transferred and endogenous antigen-specific T cells using K^d-IGRP tetramers, and measured IFN-g production by intracellular staining ex vivo.

Results

Following liposome treatment, transferred IGRP-specific $CD8^+$ T cells expanded at day 4 and contracted by day 10. IFN-g production was decreased in IGRP-specific $CD8^+$ T cells in mice that received peptide and calcitriol containing liposomes. In an accelerated transfer model of diabetes, liposome treatment was able to significantly delay the onset of diabetes.

Conclusion

These data complement studies of immunotherapy to prevent or treat Type 1 Diabetes.

AUTO1-0083
BIOSIMILAR AND ALTERNATIVES

A BIOCOMPATIBLE GOLD-CONTAINING REAGENT SUPPRESSES MACROPHAGE MEDIATED INFLAMMATION VIA INHIBITING NF-KB ACTIVATION TO AMELIORATE RHEUMATOID ARTHRITIS WITH EXCELLENT BIO-SAFETY

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Background

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases. Although the pathogenesis is complicated, macrophage mediated inflammation is at the top of clinical events and becomes the major therapeutic target. Several cytokines secreted by macrophage have been involved, such as TNF-α and IL-6. We synthesized a gold compound named SA for RA therapy aims to suppress macrophage mediated inflammation with excellent bio-safety.

Method

Macrophage Raw264.7 cells were used to evaluate the inflammation suppressing activity and underlying mechanism of SA. Secretion of cytokines was determined by ELISA detection and activation of NF-κB pathway was analyzed by immunofluorescent staining and immunoblotting. Collagen II induced arthritis in DBA/1 mice (CIA) was used to assess the RA therapeutic effects and potential toxicities *in vivio*. Inflammation index, histopathological examination and inflammatory cytokines in serum and joints were detected.

Results

Secretions of pivotal pro-inflammatory cytokines include TNF-α, IL-6 and IL-1β from activated Raw264.7 cells and CIA serum and joints were significantly inhibited by SA. The LD_{50} of SA is over 1g/kg.bw when intraperitoneal injected in mice. Inflammation in CIA mice was effectively suppressed by 5mg/kg.bw SA treating for 30 days and no obvious systemic or tissue toxicity was induced. Furthermore, the activation of NF-κB pathway was effectively suppressed by SA in both activated Raw264.7 cells and CIA joints.

Conclusion

Results indicated SA effectively suppresses inflammation in CIA mice joints with no obvious side-effects. Inhibiting activated NF-κB induced over-production of pro-inflammatory cytokines in inflammatory macrophage may contribute to this activity.

AUTO1-0191
BIOSIMILAR AND ALTERNATIVES

STATINS SHOWED CARDIOPROTECTIVE POTENTIAL IN PATIENTS WITH CONNECTIVE TISSUE DISEASES: A 28 DAYS STUDY WITH SIMVASTATIN

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Background

Connective tissue diseases (CTDs) represent the high risk for development of cardiovascular diseases. Statins a 3 Hydroxy- 3 Methyl-Glutharyl CoA reductases inhibitors proven their safety and efficacy in the treatment of atherosclerosis and atherosclerosis-related complications. In the recent years newly described non-cholesterol properties of statins may be of importance in the treatment of connective tissue diseases. To examine this we assess influence of statins treatment on heart function in patients with CTDs

Method

Patients diagnosed with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) were recruited to the study. Typical echocardiographic examination, serum levels of Il-1, Il-6, TNF-α, NT-pro BNP and ADMA were assessed twice- before and after 28 days of administration of simvastatin (20 mg/nocte).

Results

We enrolled 45 patients (15 with RA , SLE and SSc respectively). 28 days treatment was well tolerated and no drop outs were noted. Patient were characterized by the normal heart function before the study with ejection fraction (EF) (58,1± 9,2%); (62,2± 3,4%) and (63,2 ±3,6%) for SSc, RA and SLE respectively. After treatment we noted increased EF in SSc patients and significant reduction of NT-pro BNP (60,7 vs 28,1 fmol/ml; $p<0,05$) Additionally we observed reduction of IL-6 levels in SLE and RA patients (29,9 vs. 19,1pg/ml; $p<0,05$; 14,9 vs10,4pg/ml; $p<0,05$) respectively.

Conclusion

The present short study confirmed the role of statins as a valuable concomitant treatment that may be used in treatment of CTDs. 28 days treatment resulted in reduction of key inflammatory cytokine Il-6 in RA and SLE patients.

AUTO1-0607
BIOSIMILAR AND ALTERNATIVES

CHANGING LANDSCAPE IN RHEUMATOLOGY- BIOSIMILARS IN RA VS SPONDYLOARTHRITIS- TWO YEARS REAL LIFE DATA IN INDIA

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Background

"Treat to target" is the mantra for all Rheumatologists for the management of RA and Spondyloarthritis. Studies show that Biosimilar drugs work with good efficacy like their innovators. We would like to share our patients' response to Biosimilars in different arthritis.

Method

Study design: All patients since Jan 2015 who were under rheumatology care for RA, SpA and Psoriatic arthritis {PsA} (diagnosed with ACR criteria for RA, ASAS criteria for SpA) and had been on biosimilar drugs were studied and 2 years follow up data reviewed.

Results

Results: 62 patients were reviewed since the initiation of Biosimilars. Although majority of the patients 58/62 had achieved remission by 3 months (presented in Germany 2016), many patients couldn't sustain the biosimilar therapy.

We had 32 patients for this study - 17 with RA, 11 with SpA and 4 with PsA. (30 excluded)

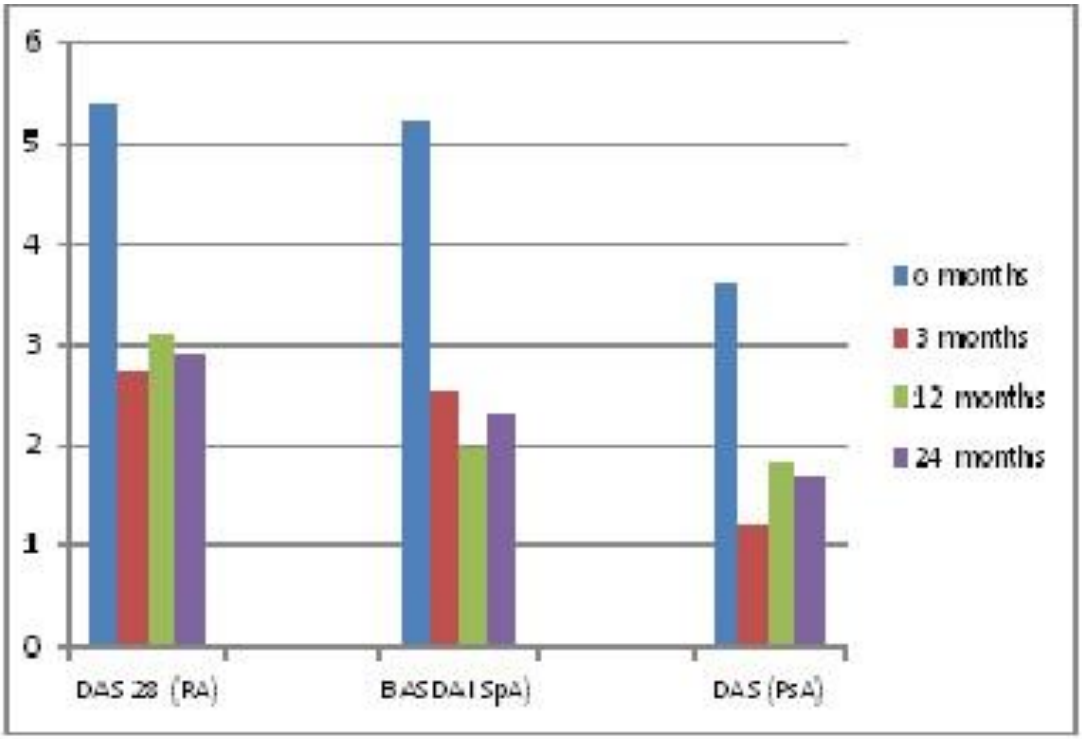

Chart showing disease activity at 0 mon (Prebiosimilar) and 3, 12, 24 months after biosimilar drugs

Classic DMARDS used were Methotrexate, leflunomide and hydroxychloroquine. 3 patients have restarted biosimilar following the flare. Biosimilar retention rate was 4/17 in RA, 3/11 in SpA and 1/4 in PsA.(so total 8/32). 5 patients with RA had rituximab and in remission.

Common biosimilars used include Exemptia, Adelirel and Adfrar (Adalimumab), Intascept, (Etanercept) and Rituxrel, Reditux RA (Rituximab). Poor Bio retention was due to the high cost.

Conclusion

Biosimilar drugs have better efficacy in RA, Spondyloarthritis, psoriatic arthritis. Rtiuximab seems to maintain remission for 2 years. Combining cDMARDs with Biosimilars has maintained the low disease activity.

AUTO1-0979
BIOSIMILAR AND ALTERNATIVES

THE GRAND DEBATE : BIOLOGICALS vs. BIOSIMILARS ? VISIONARY EXTRAPOLATION TOWARDS 'BIOBETTER' BIOTHERAPEUTICS

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Background

India is home to many biosimilars legally exported to several countries East and West. A silent revolution is in the offing as we address the challenge of treating complex rheumatic disorders to minimize mortality and morbidity substantially. Debilitating deformities, wheelchair usage, joint replacements, ICU admissions are on the decline. With growing confidence over phobia of adverse effects biosimilars provide us a launch platform to treat large number of patients afflicted by complex autoimmune diseases be they seropositive or seronegative spondarthropathies children included.

- Are we prepared to address upcoming issues upfront ?
- Will the next decade witness mass usage of biosimilars ? Even as many physicians are still shy to prescribe biologics when clearly indicated.
- Are most physicians hesitant to prescribe biologics as *induction therapy* at a stage earlier than later?
- Can physicians be bold to experiment *low dose* biosimilars as diseases unfold to progress ?
- With hands-on experience gained can physicians *tailor* biosimilar dose, frequency, shortened duration, specific to each patient ?

Can physicians thus sensitize researchers and biocorporations to evolve simpler manufacturing, quality monitored, temperature control transport systems ensuring precision and value-for-money prices ?

As therapeutics nihilism seems giving way to optimism, authorities may relent to evolve realistic regulations encouraging industry investment. The initiative rests with physicians to adapt biologicals to biosimilars towards (‘*biobetter’)* biotherapeutics to practice *P4* Rheumatology **:** Predictive, Preventive, Personalized, Participative.

Method

Scientific review of literature.

Results

NIL

Conclusion

Enhancing cost-effectiveness of Biosimilars will lead to Biobetter P4 Rheumatology.

AUTO1-0866
BIOSIMILAR AND ALTERNATIVES

TREATMENT OF ADULT PATIENTS WITH MINIMAL CHANGE DISEASE WITHOUT STEROIDS: THE BIOLOGICAL APPROACH

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Background

Minimal change disease (MCD) accounts for 15-20 % of adult nephrotic syndrome cases. In adults, data about the efficacy of RTX for MCD is limited. It is still not clear whether RTX is best used to induce remission or to maintain it, what the optimal dose should be and whether repeated doses improve response rates and prolong remission. We report a monocentric experience on the use of RTX in adult biopsy-proven MCD.

Method

Our series includes 5 adult patients, treated with RTX (4 weekly/doses of RTX 375mg/m2). 3 pts with major risk factors precluding corticosteroids or conventional immunosuppression received RTX as a first-line treatment.

Results

Proteinuria decreased from 8.4 (19.5-4.8) g/24 h to 0.03 g/24 h after 6 months; creatinine decreased from 1.44 mg/dl to 0.86 mg/l. 3 pts achieved a complete renal remission, in 1 patient proteinuria decreased by 50%. 1 patient didn't achieve any response at 10 months; a new biopsy showed a focal-segmental-glomerulosclerosis. RTX successfully depleted CD19-lymphocytes in 100% of patientss for at least 6 months. The follow-up ranged from 3 months to 24 months.

Conclusion

Our study shows a sustained efficacy of RTX in treatment of MCD. RTX can be an alternative as induction therapy or to manage recurrent forms of MCD. RTX may be preferentially used in pts at a high risk of development of the adverse effects of corticosteroids and should be considered as an important treatment alternative in patients with recurrent nephrotic syndrome. Randomized controlled trials are needed to confirmed our observations.

AUTO1-0929
BIOSIMILAR AND ALTERNATIVES

SELF ESTEEM AND PUNISHMENT BEHAVIOR OF CRIMINALS IN HYDERABAD JAIL

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Background

Self-esteem is an essential human need that is vital for survival and normal, healthy development. It arises automatically from within based on a person's beliefs and consciousness. Punishment is often mistakenly confused
with negative reinforcement. Reinforcement always increases the chances that a behavior will occur and punishment always decreases the chance of occurrence of crime.

Method

RESEARCH DESIGN

The present study was an purposive survey research. Survey conducted through standardized questionnaires.

SAMPLE

there were 20 male participants taken from central jail Hyderabad. A total of 20 questionnaires were administered on criminal participants. the age of the participants range from 22 to 40 years. They were belonging from Hyderabad Pakistan.

INSTRUMENTS

Two scales were used:

1) Self-esteem Inventory (SEI)

The self-esteem test is 25-items scale that measures the level of presence of self-esteem in individuals. It was developed by Cooper Smith (1975)

2) Punishment Attitude Scale (PAS)

Punishment attitude scale was developed by Muniza HAQUE (2003). It measure attitude towards punishment to criminals. It consists of 4 sub scales i.e.: Deterrence, Retribution, Social, Attribution of crime.

Results

Participants	Mean	S.D
Self-esteem	13.49	16.73

Mean value is less indicating low self-esteem of criminals

Table # 2

Participants	Mean	S.D	t.Test

Deterrence	38.47	12.42	5.61
Retribution	46.73	13.51	

Participants	Mean	S.D	t.Test
Social Attribution	39.22	14.33	4.20
Person Attribution	32.84	13.74	

t-values show significant difference between deterrence and retributive effects of among criminals. Hypothesis no 2 is accepted because criminals score low on deterrence.

Conclusion

Low score on self-esteem and low score on punishment increase criminal behavior and also increase crime rate.

AUTO1-0141
BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 2

ANTI-COMPLEMENT FACTOR H AUTOANTIBODIES IN AUTOIMMUNE INFLAMMATORY MYOPATHIES.

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Background

Inflammatory myopathies are a group of immune-mediated systemic disorders affecting chiefly muscles. The complement system seems to be involved in some subtypes in which presence of C5b-9 deposits are found in muscles. The aim of the study was to assess the presence of autoantibodies targeting the regulatory protein Complement Factor H (CFH), on a large cohort of myositis and to study their implication in the pathophysiology of inflammatory myopathies.

Method

Samples from 230 adults and 30 children presenting with clinical and biological criteria of inflammatory myopathies have been studied. ELISA methods were used to search for anti-CFH autoantibodies of IgG, IgM and IgA isotypes. Their binding sites were studied by competitive ELISA assay using monoclonal anti-CFH antibodies. Functional consequences of anti-CFH antibodies were studied by hemolytic assay. CFH and CFHRs genes expression were analyzed by qPCR on RNA extracted from muscle biopsies.

Results

Anti-CFH autoantibodies have been found in 50% and 43% of pediatric and adult myositis cohorts, respectively. These antibodies targeted functional domains of CFH. They neutralized CFH by forming immune complexes. Anti-CFH antibodies impacted also surface cell protection capacity of CFH. CFH was overexpressed in muscle biopsies from patients with inclusion body myositis, in whom CIC-FH titers were the highest.

Conclusion

This is the first description of anti-CFH autoantibodies in inflammatory myopathies. Hence, their presence could become a diagnostic and prognostic marker. The study of complement in inflammatory myopathies could open new therapeutic ways targeting complement activation.

AUTO1-0604
BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 2

USE OF THYMUS STEM CELL IMPLANT IN SOME AUTOIMMUNE DISEASES

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Background

In recent years, the number of autoimmune diseases has increased significantly, due to the development of civilization. This is causing the damage to the immune system.

Our research in the past few years has discovered, that after reaching puberty thymus does not disappear and is active until the end of our lives. It only decreases its volume and occurs in the form of tiny particles scattered in adipose tissue. Throughout its lifetime it continues to produce the Thymosin alpha 1. Thymus is a very important organ of immune system and is responsible for our health. Life without the thymus ends with death. It is responsible for the production of Thymosin alpha1, and for the development and differentiation of T-lymphocytes. More than 30% of the incurable diseases associated with immune deficiencies can develop, if thymus is damaged. It includes conditions such as collagenosis, ulcerative colitis, Lesniewski-Crohn, Hashimoto's disease, etc. Our research has shown that if the serum level of Thymosin alfa1 is small and ranges from 2 to 10mg / dL, then we have a good chance of developing these diseases.

Method

Our team managed to grow thymus stem cells and successfully use them in curing autoimmunity diseases. I

Results

If we want to treat any of the diseases, we need to reconstruct thymus.mplantation of about 100 million live cells causes them to start production of alpha 1-Timosine.

Conclusion

It is our opinion, that it may be the best and unique way to fight the diseases that result from immune system failure.

AUTO1-0103
BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 2

RELATIONSHIP BETWEEN NATURAL KILLER CELLS AND CIRCULATING ENDOTHELIAL CELLS BEFORE AND AFTER ENDOVASCULAR AORTIC ANEURYSM REPAIR

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Background

It is assumed that immune and autoimmune reactions can play a role in the development and progression of abdominal aortic aneurysms (AAA). The aim of this study was to assess the content of circulating natural killer cells (NK) in the pre- and postoperative period of endovascular aneurysm repair (EVAR) of AAA and its comparison with the level of circulating endothelial cells (CEC).

Method

NK and CEC were counted by flow cytometry in blood samples of patients before EVAR, within 2 weeks and in 6 months after the operation. Markers (CD16 + CD56 +) and (CD146 + CD45-), respectively, were used to identify NK and CEC.

Results

CEC levels in patients with AAA are significantly increased in comparison with healthy donors (22.1 +2.9 cells /μl and 3.0 + 0.5 cells /μl, respectively). In the early postoperative period, a slight insignificant decrease in CEC levels was observed. However in the remote postoperative period a statistically significant decrease in the level of the CEC was detected ($p < 0.05$). The level of NK in early postoperative period was significantly decreased compared to the preoperative level (212.9 + 23.6 cells/μl and 326.5 + 30.3 cells/μl, respectively, $p < 0.05$) and returned to the basal level in the long-term postoperative period. A negative correlation was found between NK and CEC after EVAR ($r = -0.440$, $p < 0.02$).

Conclusion

The obtained data confirm participation of innate immunity in the reparative process after endovascular correction of AAA and point to new therapeutic targets in this disease.

AUTO1-0085
BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 2

MESENCHYMAL STEM CELLS FROM ADIPOSE TISSUE SECRETE FACTORS WHICH DECREASE TH17 AND INCREASE TREG PERCENTAGE IN PBMCS DERIVED FROM RHEUMATOID ARTHRITIS PATIENTS

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Background

In line of their role in regenerative processes, mesenchymal stem cells (MSCs) have a well known immunosuppressive effect that raises the question about their use as a therapeutic tool in autoimmune diseases. It's largely accepted that suppression by MSCs is realized by contact and secretory mechanisms. Since the Tregs and Th17 ratio is a key factor in the pathogenesis of autoimmune disorders, we examined the secretory effect of isolated and cultured adipose derived MSCs (AT-MSCs) (12 cultures) on the percentage of Th17 and Tregs in PBMCs isolated from 12 patients with rheumatoid arthritis according the ACR/ EULAR 2010 criteria.

Method

For this purpose we used well established and published protocols for isolation and culturing of AT-MSCs and Ficoll gradient isolation of PBMCs and we cultured the PBMCs in AT-MSCs media. Flow cytometry was used for detection of Th17 markers (of CD3, CD4, CD161, CD196) and Treg markers (CD4, CD25, FoxP3) as well as ELISA for testing the cytokines secreted by AT-MSCs (IL-10, IL-4, TNFα, CCL-2, CCL-5, IFNγ, IL-6, IL-8, IL-17, IL-1b)

Results

The results demonstrated that under the action of AT-MSCs media on the PBMCs, a reduced number of Th17 was determined as well as an increased percentage of Tregs. We detected CCL-2, CCL-5 and IL-6 secretion, which could be related to the observed effect.

Conclusion

It's important to be point out that especially significant was the reduction of the $CD4+CD25^{negative}$ FoxP3+ fraction, which raised the question about the role of these cells in the Th17 / Treg context.

AUTO1-0029
BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 2

THE P140 PEPTIDE AS A MODULATOR OF AUTOPHAGY IN AUTOIMMUNE AND INFLAMMATORY DISEASES

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Background

Nowadays, pharmacologic treatments of inflammatory and autoimmune diseases are largely palliative rather than curative. Most of them result in non-specific immunosuppression, which can be associated with disruption of natural and induced immunity with significant, sometimes dramatic, adverse effects.

Method

Among the novel strategies that are under development, tools that modulate the immune system to restore normal tolerance mechanisms, are central. In these approaches, peptide therapeutics constitute a class of agents that display many physicochemical advantages. Within this class of potent drugs, the phosphopeptide P140 is very promising for treating patients with SLE, and likely also patients with other chronic inflammatory diseases.

Results

In a multicenter, randomized, placebo-controlled phase-IIb study for lupus, P140/Lupuzor™ was found to be safe and met its primary efficacy end points, confirming pre-clinical data generated in MRL/lpr lupus-prone mice. Lupuzor is currently evaluated in phase-III clinical trials in the US, Europe and Mauritius. We discovered that P140 targets autophagy, a finely orchestrated catabolic process, involved in the regulation of inflammation and in the biology of immune cells. P140 acts directly on a particular form of autophagy called chaperone-mediated autophagy, which is hyperactivated in lupus in certain subsets of lymphocytes. The “correcting” effect of P140 on autophagy results in a weaker signaling of autoreactive T cells, leading to a significant improvement of physiopathological status of treated mice.

Conclusion

These findings open novel avenues of therapeutic intervention in other pathological conditions in which reduction of autophagy activity would be desired. New data will be presented in the context of neurological autoinflammatory diseases.

AUTO1-0148
BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 2

AUTOIMMUNE PHENOMENA DUE TO IMMUNE CHECK-POINT INHIBITORS. AN EXTENSIVE REVIEW AND TREATMENT STRATEGY

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Background

The discovery and approved treatment with immune checkpoint inhibitors (ICIs) for metastatic cancer patients has dramatically improved survival. Despite the obvious benefits, and as a result of manipulation of the immune system, immune-related adverse effects (irAEs) have appeared.

Method

We performed an extensive search of the medical literature for irAEs including autoimmune phenomena, organ-specific disease and classic autoimmune diseases. In addition, we reviewed the treatment algorithms for such cases.

Results

Organ involvement included: dermatologic, especially vitiligo, self-limited dermatitis (44%); gastrointestinal, diarrhea, colitis similar to Crohn's disease (35%); endocrine, more commonly hypothyroidism than hyperthyroidism (6%); and hepatic, hepatitis (5%). Neurologic, hematologic, and ophthalmologic irAEs, were much less common. By the specific ICI drug, after ipilimumab therapy, the most common adverse event was gastrointestinal like colitis, hepatitis, pancreatitis (39.7%), followed by endocrine irAEs such as hypophysitis, thyrotoxicosis, hypothyroidism, and central adrenal insufficiency (29.1%). After pembrolizumab therapy, cutaneous irAEs were rash, pruritus, vitiligo and dermatitis were the most documented (30%). After nivolumab therapy, endocrine and pneumonitis irAEs were reported equally (42.9%).

The development of de novo classic autoimmune disease including lupus, rheumatoid arthritis, and myositis were described in case reports. In patients with prior autoimmune diseases, exacerbations were more common in the presence of active disease.

Therapy for autoimmune events included prednisone, while biologics or discontinuation of ICI therapy were reserved for severe adverse effects.**Conclusion**

Many autoimmune phenomena predominantly organ-specific and not the development of classic autoimmune disease are described in patients treated with ICI. Collaboration between oncologists and rheumatologists is essential.

AUTO1-0466
CANCER AND AUTOIMMUNITY

CANCER IMMUNOTHERAPIES AND ENDOCRINE AUTOIMMUNE DYSFUNCTIONS

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Background

Cancer immunotherapies have been approved recently, as immune checkpoint inhibitors (ChekIN): ipilimumab (CTLA-4 antagonist), nivolumab and pembrolizumab (PD-1 antagonists), and atezolizumab (PD-L1 antagonist). ChekIN engage T lymphocytes (Treg and PD-1^+ T-cells), and treat the immune system, regardless of cancer histology or presence of driver mutations.

Method

We searched the literature on PubMed for cancer immunotherapy, endocrine dysfunctions, and thyroid cancer (TC), in humans.

Results

Immune-related endocrine toxicities [hypophysitis, thyroid dysfunction (ThyDysf), adrenal insufficiency and type 1 diabetes mellitus] are the most frequent, they are due to an autoimmune reaction and in 50% of cases are irreversible. ThyDysf (as thyrotoxicosis, hypothyroidism, or painless thyroiditis), occur in 1–10% of ChekIN-treated patients. ChekIN-treated patients, with previously diagnosed autoimmune thyroid disorders (AITD), or circulating AbTg, AbTPO, more frequently develop thyroiditis. Patients with anti-thyroid Ab show a higher tumor response, suggesting an association between inflammatory and tumor response. Few studies evaluated immunotherapies in TC; however, one case of anaplastic thyroid cancer treated with vemurafenib and nivolumab showed substantial regression and complete remission.

Conclusion

ChekIN therapy is associated with many autoimmune endocrine dysfunctions, as reported above. Further studies in TC patients are necessary to evaluate the use of ChekIN in aggressive TC.

AUTO1-0429
CANCER AND AUTOIMMUNITY

THYMIC EPITHELIAL TUMORS (TET), OPPORTUNISTIC INFECTIONS AND AUTOIMMUNITY

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Background

Bellanti (Immunology IV, 2012) depicts a quintet of immune disregulation-based disorders, one of which is susceptibility to infection. This is not surprising, since T-cell role of eliminating invading organisms is hampered by deficient thymic training .This entails frequent infections, where opportunistic organisms stand out. TET patients are prone to infections and may contract several different organisms. This situation often coined "Good's syndrome", may manifest hypogammaglobulinemia, may accompany TET.

Method

Thymomas subtypes were defined by WHO 2004 classification. Myasthenia gravis (MG) was monitored serologically. Microbiology was done in-house; samples for Mycobacterial culture were sent to the MOH National Laboratory.

Results

None of the patients presented herein showed hypogammaglobulinemia ; in all cases infections were due to cellular, T-(and B-) cell deficiency. One case was afflicted with pulmonary and cerebral Nocardia . Another patient has had recurrent sinobronchial infections, P. auroginosa was isolated Later on this organism caused a severe sepsis. This patient had also mucocutaneous candidaiasis. Mycobacterium simiae grew, twice, from a sputum culture. Additional patient had Good syndrome: a life-threatening sepsis following diarrhoea and underwent small-bowel resection. Later in the course he had viral (CMV) myeloencephalitis. All patients had symptomatic MG as well as active neoplasm.

Conclusion

.This case series suggests that patients with recurrent thymoma and MG are a risk group f0r opportunistic infections Risk Assessement is a challange due to confounding factors (e.g. corticosteroid therapy) We are planning a study of post-operative Herpes zoster in thymoma patients, compared to non-TET operated patients in order to better assess this risk.

AUTO1-0705
CANCER AND AUTOIMMUNITY

WHICH ROLE FOR IMMUNOGLOBULIN IN PATIENTS WITH CANCER?

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Human immunoglobulin (Ig), firstly used as replacement therapy in primary immunodeficiencies, has been given successfully to patients with different autoimmune diseases (AID). Available commercial preparations encompass polyclonal IgG pooled from sera of thousands of donors which can be administrated by the intravenous (IVIg) or subcutaneous (SCIg) route. Several mechanisms of action have been proposed to explain the mechanisms of IVIg-mediated immunomodulation, accordingly to the nature of the disease. The immunodulatory role of SCIg is not completely understood. Among the different properties of human Ig, it is possible to speculate about an immunomodulatory role even for patients with cancer. Natural antibodies in human Ig can have anti-tumorigenic functions that act especially on tumour spread. We presented a case of a patient (M/60 ys) with common variable immunodeficiency treated with IVIg 400 mg/kg monthly, then shifted to 20%SCIg (30 g/kg/week) for a major cardiovascular event. He was diagnosed with pancreatic cancer involving the isthmus and the body with diffusion to mediastinic lymph nodes. The prognosis was extremely severe. He received chemotherapy with Irinotecan, 5-fluorouracil and folinic acid while continuing 20%SCIg therapy. Eleven months after, he died for massive disease diffusion. The treatment allowed him a longer survival; it is possible that Ig therapy lessen the disease spread and death. This anti tumorigenic function of Ig may represent a powerful adjuvant for inhibition of tumor spread. However, more data are needed to establish definitive conclusions.

AUTO1-0091
CANCER AND AUTOIMMUNITY

HYPOTHESE ROLE OF THE STINGS OF SIMULIES ON THE EMERGENCE OF THE AUTOIMMUNE DISEASES AND THE PREVENTION THERE DIETHYCARBAMAZINE

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Background

A therapeutic experiment was practised on three people with diethylcarbamazine. This molecule proved to be effective on clinical symptomatology in the syndrome of the chronic asthenia, the fibromyalgia and the syndrome of the legs without rest. From that, I built a working hypothesis which I would like proven, with the implementation of certain means.

Method

A) To highlight the immunogenic component, injects at the time of the puncture by this cosmopolitan hematophagous insect, the simulie; potential vector of parasites such as filariaes

B) To prove that this component is a part of secretions of the digestive tract of the simulie.

C) To prove that this component probably a glycoprotein is responsible for one hyper activation of the macrophages involving of the immunizing disorders, like those found in the fasciite with macrophages.

D) To prove that the beneficial effect of the diethylcarbamazine is due to its direct action on this component, by a lytic effect are equivalent to the lytic effect that this molecule exerts on the wall of the microfilariae by lysing it.

Results

To establish a link between this components circulating in the human body, and the generated immunizing deregulation, and to understand the mechanisms on the emergence of the autoimmune diseases, like on the facilitation of the development of certain cancers. If the first approaches are conclusive, to apprehend, possible extent of the impacts to all the bodies.

Conclusion

The purpose of my approach is not to be made a fool but to convince research teams to work on new tracks

AUTO1-0389
CANCER AND AUTOIMMUNITY

THE BEAUTY AND THE BEAST: NATURAL HUMAN ANTIBODY VARIABLE REGION GENES TURNED INTO CHIMERIC ANTIGEN RECEPTORS ON T CELLS HELP TO BEAT CANCER

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Background

As an approach to reveal new biomarkers on cancer cells, we performed a careful analysis of the natural human antibody repertoire in the cancerous tissue and set up a cancer targeting strategy.

Method

Heavy (VH) and light chain (VL) Immunoglobulin (Ig) variable region-genes were amplified, using specific primers from breast cancer and melanoma. We made comparative DNA sequence analysis of Ig VH and VL genes and constructed single chain Fv (scFv) antibody fragments. We generated scFv phage display libraries and tested them against native cancer cell membrane preparations. Column purified Ig preparative fractions obtained from a melanoma patient were tested against sialylated glycosphingolipids in enzyme-linked immunosorbence assay (ELISA). Chimeric antigen receptor (CAR) constructs were designed with specific antibody fragments.

Results

Tumorassociated disialylated glycosphingolipid (GD3) antigen-binding antibody fragments of human origin were defined. GD3 ganglioside binding autoantibodies could be verified from the peripheral blood of the melanoma patient. TIL-B originated anti GD3 scFv coding DNA sequences were engineered into new CAR constructs, using the Sleeping Beauty transposon system to introduce the CAR to redirect T cells to cancer cells. HEK293 and immune T cells were successfully transduced with GD3 CAR constructs.

Conclusion

The natural humoral immune reponse of patients with cancer can be harnessed to reveal uniquely tumorassociated disialylated glycosphingolipids that paves the way for a novel GD3- specific CAR–T cell-engineering gateway technology and serves as new cancer treatment possibility. Acknowledgements: Fulbright No1214104, Fulbright No1206103 Grants, SPORE MDACC LJN Cooper, Harry J. Lloyd Charitable Trust Melanoma Research Award, OTKA T048933 Grant

AUTO1-0616
CANCER AND AUTOIMMUNITY

IMMUNE CHECKPOINT INHIBITORS IN CANCER AND AUTOIMMUNITY

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Background

Abstract

Background: The use of immune checkpoint inhibitors (ICI) has grown incessantly since they were first approved in 2014. These monoclonal antibodies inhibit T cell activation, yielding a dramatic tumor response with improved survival. However, immunotherapy is frequently hampered by immune adverse events (iAE) such as hypophysitis, colitis, hepatitis, pneumonitis and rash. Until recently, rheumatic side effects were only infrequently reported.

Aim: To describe the rheumatic manifestations encountered among patients treated with ICIs in a large tertiary cancer center in Israel

Method

Methods: The cancer center's patient registry was screened for patients who had ever been treated with ipilimumab, pembrolizumab and/or nivolumab with relevant data gathered from clinical charts.

Results **Results**: Rheumatic manifestations were encountered in 3.5% of patients who had received immunotherapy between January 1st 2013 and April 30th, 2017. The most common rheumatic manifestation was inflammatory arthritis (85%) for which a third had a clear cut predisposing factor. Treatment with NSAIDS was mostly unsuccessful while steroid therapy was beneficial in doses ≥20 mg/d. Methotrexate enabled steroid tapering without an excess of side effects or tumor progression in the short follow-up available.
Conclusion

Conclusions: Our findings underscore that rheumatic iAE are part of the side effect profile of ICIs and require heightened awareness as these therapies are becoming the standard of care for various malignancies. We show that these appear later in the course of iAEs and respond preferentially to high dose steroids. MTX appears effective as a steroid sparing agent.

AUTO1-0507
CANCER AND AUTOIMMUNITY

RADIATION THERAPY OF BREAST CANCER IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis (SSc) is a rare autoimmune disorder, whose links with cancer are currently under investigation around the world. Notably, a subgroup of SSc is now considered as related to breast cancer. Radiation therapy has a key role in the management of numerous cancer, but is usually considered as deleterious in SSc. Indeed, radiation therapy and SSc share some common mechanisms, such as reactive oxygen species production, fibroblast proliferation and endothelial damages. So, radiation therapy could worsen fibrotic process in SSc. Herein, we aimed at describing the tolerance of radiation therapy in SSc patients with breast cancer.

Method

We conducted a retrospective study at the Montpellier University Hospital and included SSc patients followed between 2003 and 2017.

Results

We identified 55 patients with SSc and at least one cancer. Fifteen patients were carefully treated with radiation therapy for breast cancer, including 6 patients a few months (2-10 mo) after SSc diagnosis. In these patients, radiation therapy was well tolerated, and no severe (early or late) toxicity was observed according to CTCAE v4.0 criteria. However, three patients had asymptomatic interstitial pneumonia on CT-scan and one patient had dermal fibrosis within the irradiation fields.

Conclusion

Tolerance of breast irradiation in patients with breast cancer is difficult to assess, but careful selection of patients and use of radiation therapy (considering radiation-induced lymphocyte apoptosis assay, doses, and irradiation zones) may prevent from severe toxicity.

AUTO1-0589
CANCER AND AUTOIMMUNITY

NOVEL MOUSE MODEL CHARACTERIZATION AND HUMAN RNA PROFILING REVEAL ESTROGEN-INDEPENDENT INFLAMMATORY MECHANISMS IN AROMATASE INHIBITOR INDUCED ARTHRALGIA

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Background

Aromatase Inhibitor Induced Arthralgia (AIIA) is a painful inflammatory condition that occurs in half of all breast cancer patients taking aromatase inhibitors (AIs). Additionally, 20% of AIIA patients suspend medication completely due to the painful symptoms associated with this condition, which negatively influences patient prognosis and survival. Since the pathogenesis is not known, our objective was to create and AIIA mouse model and to validate these results in human samples.

Method

Female BALB/C-Tg(NFκB-RE-luc)-Xen mice, which have a firefly luciferase cDNA reporter gene under the regulation κB binding sites, were oophorectomized and treated with AI (letrozole) by daily subcutaneous injections for 5 weeks. The primary weight-bearing joint (hind limb) was examined histopathologically and NFκB activity was measured by bioluminescent imaging. Serum was collected for cytokine analysis. Healthy human PBMCs were treated with letrozole, estrogen, or both and cellular RNA sequencing was performed at 24 hours.

Results

Oophorectomized mice injected with AIs showed enhanced MRI and bioluminescent imaging signals and significantly elevated serum cytokine levels of IL-2, IL-4, IL-6, and CXCL1. Furthermore, infiltrates were detected in the tendons and surrounding muscle tissue. Surprisingly, the same up-regulation and imaging results were observed in AI-treated mice without oophorectomy, which indicated an estrogen-independent inflammatory response. RNA sequencing of human PBMCs revealed a collection of unique inflammatory pathways and genes associated with the treatment of letrozole, estrogen, or both.

Conclusion

These results establish a novel AIIA mouse model and identify estrogen-independent inflammatory pathways that will be targeted therapeutically in future studies to potentially inhibit this adverse inflammatory burden.

AUTO1-0459
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

THE HLA CLASS II RISK GENES ASSOCIATED TO CELIAC DISEASE ARE PREFERENTIALLY EXPRESSED COMPARED TO NON-ASSOCIATED HLA GENES: IMPLICATION FOR THE PATHOGENIC ANTI-GLUTEN T-CELL RESPONSE

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Background

The DQA1*05 and DQB1*02 (DQ2.5) genes conferring susceptibility to celiac disease can be carried on chromosome 6 either in *cis* (DR3/DRX) or *trans* (DR5/DR7) configurations. We have recently found that specialized Antigen Presenting Cells (APC) carrying the DQ2.5 genes in homozygosis (DR3-DR3 haplotype) or in heterozygosis (DR1-DR3 haplotype) show similar amount of DQ2.5 mRNA and encoded heterodimers, and that the DQ2.5 genes expression is consistently higher respect to that of non-disease associated alleles (Pisapia et al., 2016).

Method

We compared the quantity of DQA1* and DQB1* mRNAs, by RT-qPCR, and of proteins, by flow cytometry, in DR5/DR7 respect to DR1-DR3 APCs.

Results

Similarly to the *cis* configuration findings, we observed that in DR5/DR7 cells the DQA1*05 and DQB1*02 risk alleles were more expressed than the non-CD predisposing alleles, either in celiac patients and healthy controls. However, the differential expression between CD-associated and non-associated alleles was much stronger in APC from celiac patients that non-affected subjects. These results were further confirmed by quantification of DQα105 and DQβ102 proteins by specific monoclonal antibodies and validated by functional experiments with intestinal T cells.

Conclusion

Our findings clearly indicated that the expression of HLA class II risk genes strongly influence the pathogenic autoimmune response in celiac disease. Moreover, these results suggest that the high expression of predisposing alleles may favour the establishment of autoimmunity.

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AUTO1-0387
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

IDENTIFICATION OF CHITINASE 3 LIKE-1-PROTEIN AS A NEUTROPHIL AUTOANTIGENIC TARGET IN INFLAMMATORY BOWEL DISEASES AND AUTOIMMUNE LIVER DISORDERS

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Background

Chitinase 3-like-1 (CHI3L1) also referred to as YKL-40 is a 40 kDa protein belonging to the 18-glycosylhydrolase family with no chitinase activity. It was reported that CHI3L1 plays an important role in various types of cancer and other diseases characterized by inflammation including rheumatoid arthritis, inflammatory bowel disease (IBD) or autoimmune liver diseases. Noteworthy, it interacts with the intestinal microbiota including enteropathogenic bacteria. The aim of the study was to investigate the potential role of CHI3L1 as autoantigenic target in IBD and autoimmune liver diseases.

Method

Recombinant CHI3L1 was used as solid-phase antigen for the detection of CHI3L1 autoantibodies (CHI1L3Ab) in enzyme-linked immunosorbent assay (ELISA). One hundred ten patients with Crohn's Disease (CD), 95 with ulcerative colitis (UC), 23 with primary sclerosing cholangitis (PSC), 126 with celiac disease (CeD) and 19 with autoimmune hepatitis (AIH) as well as 86 healthy controls (HC) were analyzed for the occurrence of CHI1L3Ab IgG, IgA, and secretory IgA (sIgA) by ELISA.

Results

Patients with CD demonstrated significantly higher prevalences of CHI1L3Ab IgA, and sIgA in contrast to HC (28/110, 46/110 vs. 2/86; p = < 0.0001, < 0.0001, respectively). Further, CHI1L3Ab IgA and sIgA were significantly less prevalent in patients with UC and CeD than in those with CD. Of note, patients with AIH revealed a higher prevalence of CHI1L3Ab IgG, and sIgA compared with HC (10/19, 6/19 vs. 2/86, p < 0.0001, = 0.0022, respectively).

Conclusion

CHI3L1 is a novel biomarker for IBD and autoimmune liver diseases.

AUTO1-0168
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

THE ANCIENT WHEAT SPECIES TRITICUM MONOCOCCUM HAS A REDUCED IN VIVO IMMUNOGENICITY: IMPLICATION FOR CELIAC DISEASE PREVENTION

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Background

In the recent time there is an increasing interest to find wheat varieties with null, or low toxicity, for treatment or prevention of celiac disease. *T. monococcum*, a diploid (AA genome) ancient wheat is a promising species for the low content of gluten epitopes and the high *in vitro* digestibility. However, very little is known on the *in vivo* immunogenicity of *T. monococcum* for celiacs.

Method

We used a short (3 days) wheat challenge (SGC) to assess the *in vivo* immunostimulatory properties of gluten from either *T. monococcum* (*ID331* cultivar) and the hexaploid wheat *T. aestivum* (*Sagittario* cultivar), as control wheat. Seventeen celiacs (aged 6-14yrs) in disease remission participated to the study and consumed 3 sandwiches/day with control (N=7) or monococcum wheat (N=10), corresponding to approximately 12 gr of gluten/day. Immune-reactivity was assessed by counting the IFN-γ-secreting cells in the blood reactive to whole gliadin or to dominant gliadin peptides.

Results

The SGC with common wheat mobilized in peripheral blood a remarkable number of IFN-γ-secreting cells in response to either hexaploid gliadin and dominant peptides ($p<0.05$). Conversely, diploid monococcum wheat elicited a very low number of T cells releasing IFN-γ in response to gliadin and peptides (p=ns).

Conclusion

In conclusion, ancient diploid wheat showed a reduced *in vivo* capability to activate in celiac patients T cell response compared to common cereal. Although *T. monococcum* is a cereal not suitable for the diet of celiacs, it still could have a role in strategies aimed to prevent celiac disease in at risk subjects.

AUTO1-0253
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

DIFFERENT DENSITIES OF IL4-PRODUCING CELLS AND OF TCR ΓΔ+ CELLS IN INTESTINAL MUCOSA OF POTENTIAL AND ACUTE CELIAC DISEASE: BIOMARKERS FOR COELIAC DISEASE DIAGNOSIS

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Background

Coeliac disease (CD) is characterized by a variable spectrum of symptoms and intestinal mucosa damage. Most patients show a villous atrophy (overt CD), but some show a normal mucosa despite the presence of CD-specific autoantibodies and symptoms (potential CD). However, the pathogenic mechanism leading to mucosa lesion is not completely understood. We compared the cytokine profile and the phenotype of intestinal T-cells between potential versus overt CD.

Method

Cell phenotype and cytokine production patterns were analysed by flow cytometry, in both gluten-raised T-cell lines (TCLs) and freshly isolated mucosal cells. Jejunal biopsies were obtained from 19 overt CD, 16 potential CD and 12 non-CD children.

Results

Increased number of CD3 TCR γδ+ T-cells, was found in TCLs from overt CD compared to potential CD or non-CD healthy subjects. A higher fraction of IL4-producing cells, mainly CD4+ T-cells, was detected in TCLs from children with normal mucosa, either potential CD or non-CD controls. Ex vivo analysis on freshly isolated intestinal cells confirmed the significant increased frequency of TCR γδ+ T-cells in the gut mucosa of CD children with villous atrophy. An increased expansion of IL4-producing T-cells was found in biopsies from potential CD compared to overt CD patients.

Conclusion

Our study confirms an expansion of TCR γδ+ T-cells in coeliac gut mucosa compared to histologically normal mucosa. The transition to villous atrophy seems to be characterized by the disappearance of IL4+ T-cells. These findings may offer biomarkers useful to characterize the different stages of CD.

AUTO1-0119
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

MESENCHYMAL STROMAL CELLS REDUCE THE RISK O INFECTIOUS COMPLICATIONS IN PATIENTS WITH ULCERATIVE COLITIS, RECEIVING INFLIXIMAB.

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Background

Aim. To conduct a comparative analysis of the clinical risk of mild infection or exacerbation of chronic inflammatory diseases in patients with ulcerative colitis (UC) receiving infliximab (IFX) (without immunosuppressants) and IFX + MSCs.

Method

The first group included 19 patients with UC who received IFX+MSCs. The second group included 27 patients with UC who received IFX, without immunosuppressants. Safety assessment: non-serious infectious, exacerbation of chronic inflammatory diseases.

Results

During two years of follow-up in the first group of infectious complications were detected in 1 patient (5.3%) of 19, the second in 5 (18.5%) out of 27 (OR-0.28; 95% CI 0.04-2.24; p=0.37).

After 3 years - in the first group of non-serious infectious and development or exacerbation of chronic inflammatory diseases observed in 2 (10.5%), the second in 12 (44.1%), which was significantly higher than 1-th group (OR-0.24; 95% CI 0.06-0.94; p=0.032).

After 4 years- in the first group of non-serious infectious complications development or exacerbation of chronic inflammatory diseases observed in 4 (21.05%) , the second in 15 (55.5%), (OR-0.38; 95% CI 0.15-0.96; p=0.04).

After 5 years, in the first group or exacerbation of complications of chronic diseases 6 (31.6%) , the 2-nd in 20 (74.1%), (OR-0.43; 95% CI 0.21-0.86; p=0.001).

Conclusion

The analysis found a reduction in risk in the development of non-serious infectious complications and exacerbation of chronic inflammatory diseases in UC patients who received IFX in combination with MSCs from 3 to 5 years of observation.

AUTO1-0242
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

THE NON-CHEMOTACTIC FUNCTION OF CCR6 PROMOTES DIFFERENTIATION OF PATHOGENIC TH17 CELLS DURING GUT INFLAMMATION AND AUTOIMMUNITY.

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Background

Intestinal epithelial cells produce the increased amount of CCL20 during gut inflammation and recruit $CCR6^+$ immune cells and hyperactivation of immune cells cause inflammatory bowel disease (IBD). Since CCR6 is a G protein-coupled receptor, we hypothesized that CCR6 signaling in $CD4^+$ T cells in inflamed gut microenvironment controls plasticity and pathogenicity of Th17 cells.

Method

Peripheral blood samples were collected from ulcerative colitis (UC) patients and healthy individuals, and Th17 phenotype and plasticity were measured using flow cytometry. We induced gut inflammation in wild-type C57BL/6 or $CCR6^{-/-}$ mice by giving dextran sodium sulfate (DSS) in drinking water; and autoimmune colitis by adoptive transfer of naïve $CD4^+$ T-cells into $RAG1^{-/-}$ mice. Cells were analyzed using flow cytometry or RT-PCR.

Results

Circulating CD4 lymphocytes in peripheral blood of UC patients showed significantly increased expression of CCR6, and these $CCR6^+$ $CD4^+$ T-cells had a significantly high frequency of $RORgt^+$ Th17 and $RORgt^+T\text{-}bet^+$ Th17 cells (Th1-like Th17 cells) as compared to healthy individuals. *In vitro* activation of naive $CD4^+$ T-cells with CCL20 under Th17-polarization condition promoted Th1-like Th17 cells in a CCR6-dependent manner in mice and human. Mice with DSS-induced gut inflammation or with autoimmune colitis showed CCR6-dependent pathogenic Th1-like Th17 cell differentiation. CCL20-CCR6 activation-induced phosphorylation of Akt, mTOR and STAT3 molecules in $CCR6^+$ $CD4^+$ T-cells.

Conclusion

Our results show that CCR6 signaling during gut inflammation and autoimmune colitis promotes the differentiation inflammatory Th17 cells, and suggests that the intervention of CCR6-CCL20 signaling could potentially provide a therapeutic benefit to IBD patients.

AUTO1-0663
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

ANTIBODIES AGAINST NEO-EPITOPE OF MICROBIAL AND HUMAN TRANSGLUTAMINASES

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Background

Microbial transglutaminase (mTg) and human tissue Tg (tTg) form complexes with gliadin peptides, thus posttranslating and modifying gliadin to present neo-epitopes. **The aims** were to test the diagnostic performance of antibodies against both non-complexed and complexed forms of both transglutaminases in children with celiac disease, compared with disease controls and to correlate antibodies' levels to the degree of intestinal atrophy.

Method

Serum samples, at day of intestinal biopsy, were collected from 350 children with celiac disease (mean age 7.4 years) and 215 disease controls (mean age 10.2 years) and tested using the following ELISAs detecting IgA, IgG or both IgA+IgG combined (Check): tTG (for in house research use only), *AESKULISA*®s tTg New Generation (tTg neo-epitope (tTg-neo)) and mTg neo-epitope (mTg-neo, RUO). Results were correlated to the degree of intestinal injury, using the revised Marsh criteria.

Results

mTg-neo Check had the highest sensitivity and tTg IgA the highest specificity. Comparing the different correlations between antibodies' isotypes, the tTg Check ($r=0.7889$, $p<0.0001$) and tTg-neo Check ($r=0.7544$, $p<0.0001$) as well as tTg IgA and tTg-neo IgA ($r= 0.7571$ and $r= 0.7279$, $p<0.0001$ respectively) were the best indicators of intestinal damage in CD.

Conclusion

It is suggested that the combination of tTg-neo IgA/IgG antibodies should be recommended as a first line screening test for CD in children. The tTg and tTg-neo assays show similar diagnostic performance and are recommended as good screening tests for CD in children. mTg-neo IgG presents a new serological biomarker for celiac disease.

AUTO1-0464
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

MUCOSAL CD103+CD4+ AND CD103+CD8+T CELL SUBSETS IN THE GUT OF INFLAMMATORY BOWEL DISEASE PATIENTS AT DIAGNOSIS AND DURING FOLLOW-UP

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Background

Recently, a pro-inflammatory role has been suggested for $CD103^+CD4^+$, but not for the $CD103^+CD8^+$mucosal T-cell subset in Inflammatory Bowel Disease. As the CD103-integrin is the target of new therapies, we aimed to study the frequencies of different $CD103^+$T-cell subsets in newly diagnosed, untreated IBD-patients at baseline and during follow-up, compared to healthy controls(HC).

Method

Patients with Crohn's disease (n=75;CD), ulcerative colitis (n=49;UC) and HC (n=16) were prospectively included. On baseline and follow-up (n=54) biopsy specimens immunophenotyping was performed by flowcytometry. Mucosal-($CD103^+$) and non-mucosal($CD103^-$) T-cells were expressed as median percentages(%) of the total T-cell population ($CD3^+$) and as a proportion of $CD4^+$ or $CD8^+$T-cell subsets with corresponding interquartile range (IQR).

Results

At diagnosis IBD-patients had lower $\%CD3^+CD103^+$T-cells (11%(7-21)) compared to HC(40% (26-86),p=0.001). The $\%CD3^+CD103^+CD4^+$ was 3%(1-5) in IBD (4% of total $CD4^+$T-cells) and 5%(5-7) in HC (11% of total $CD4^+$T cells,p=0.007). The $\%CD3^+CD103^+CD8^+$ in IBD was 9%(4-15, 33% of total $CD8^+$T-cells) and in HC 42%(23-57, 83% of total $CD8^+$T-cells,p=0.001).
The majority of $CD3^+CD103^-$T-cell subsets in active IBD at baseline was represented by $CD103^-CD4^+$T-cells (65%(52-74),in HC 30%(21-50),p=0.001). When endoscopic in remission, frequencies of $CD103^+$T-cell subsets approach percentages comparable to HC.

Conclusion

Active mucosal inflammation in IBD-patients is associated with decreased percentages $CD3^+CD103^+$T-cell subsets. Endoscopic remission in IBD is associated with normalization of the mucosal T-cell profiles. The suggested pro-inflammatory $CD103^+CD4^+$T-cells represented only a minority of the total mucosal ($CD103^+$)T-cell-subset. It is mainly the $CD4^+CD103^-$T-cell subset that infiltrates the inflamed colon in IBD. These results challenge the pro-inflammatory role of these $CD103^+CD4^+$T-cells in IBD.

AUTO1-0053
CELIAC AND GASTRO INTESTINAL TRACT AUTOIMMUNITY

ANTIBODIES AGAINST ZONULIN AND OTHER TIGHT JUNCTION PROTEINS IN CELIAC DISEASE

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The intestinal or gut barrier has a vital role in maintaining the body's health. It simultaneously blocks the entry of immunogenic molecules while absorbing nutrients necessary for life. The barrier's dysfunction and/or damage can lead to inflammation, autoimmunity, and even cancer. Assessment of the barrier's health and integrity can be crucial in treating these disorders. When the barrier is damaged, the proteins that make up its tight junctions are fragmented, causing the production of antibodies against them. The antibodies to zonulin and other barrier proteins can be measured as biomarkers of the gut wall's integrity. We conducted this study to compare the efficiency of measuring the level of zonulin itself in serum versus measuring the antibodies against zonulin and other barrier proteins. Since zonulin levels have been shown to fluctuate from day to day and even hour to hour, we measured zonulin levels versus IgA and IgG antibodies against zonulin in 18 controls at 0, 6, 24 and 30 hours after blood draw. We also measured zonulin level versus antibodies against zonulin and other barrier proteins in sera from 30 controls and 30 patients with celiac disease (CD) using ELISA. In the majority of the 18 controls, zonulin levels showed significant fluctuations from sample to sample, while antibody measurement in all samples was highly stable and reproducible. Zonulin level was elevated in 37% of CD patients, while antibodies against zonulin and other barrier proteins were elevated in 86% of CD patients. Due to the fluctuation of zonulin levels, we recommend the measurement of zonulin and other barrier proteins to evaluate intestinal barrier integrity.

AUTO1-1011
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

COMPARISON OF FIVE TSH-RECEPTOR ANTIBODY ASSAYS - RESULTS FROM AN OBSERVATIONAL STUDY

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Background:
Early diagnosis and relapse prediction in Graves' disease [GD] may influence treatment. We assessed the abilities of four TSH-receptor antibody tests [TRAb] and one cAMP bioassay to predict relapse of GD.
Methods:
Observational study investigating patients presenting with GD at a Swiss hospital endocrine referral center or an associated endocrine outpatient clinic. Main outcomes were diagnosis and relapse of GD after stop of anti-thyroid drugs. We used Cox regression to study associations of TRAb levels with relapse risk and calculated area under the receiver operating characteristics curve [AUC] to assess discrimination. Blood draws took place as close as possible to treatment initiation.
Results:
ROC curve analysis revealed AUCs ranging from 0.90 (TSAb Biossay) to 0.97 (IMMULITE TSI) for the diagnosis of GD. Highest sensitivity (94.0%) was observed for IMMULITE and RSR TRAb Fast while the greatest specificity (97.9%) was found with the EliA anti-TSH-R. GD relapse was studied using Cox regression analysis comparing the highest versus the lower quartiles. The highest hazard ratio [HR] was found for BRAHMS TRAK (2.98, 95% CI 1.13 - 7.84), IMMULITE TSI (2.40, 95% CI 0.91 - 6.35), EliA anti-TSH-R (2.05, 95% CI 0.82 - 5.10), RSR Fast TRAb (1.80, 95% CI 0.73 - 4.43), followed by RSR STIMULATION (1.18, 95% CI 0.46 - 2.99). Discrimination analyses showed respective AUCs of 0.68, 0.65, 0.64, 0.64, and 0.59.
Conclusion:
The assays tested had good diagnostic power and relapse risk prediction with few differences among the new assays.

AUTO1-0262
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

MACROPHAGE EXPRESSION OF THE PEPTIDYLARGININE DEIMINASES 2 AND 4 (PAD2 AND 4), RESPONSIBLE FOR CITRULLINATION OF THE PROTEINS TARGETED BY ACPA, VARIES WITH CELL POLARISATION

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Background

We demonstrated that Rheumatoid Arthritis (RA)-associated autoantibodies to citrullinated proteins (ACPA) are produced in the synovial tissue (ST) of patients where PAD2 and 4 are probably responsible for fibrin citrullination and genesis of ACPA epitopes. In the ST, PAD2 and 4 are mainly expressed by $CD68^+$ mononuclear cells. Otherwise, we showed that the macrophages (Mϕ) generated in the presence of IFN-γ, IL-4, IL-10 or M-CSF, present various cytokine responses to ACPA-containing immune complexes.
Mϕ being candidates for cell origin of PADs in the ST, we evaluated expression of PAD2 and 4 by Mϕ polarised to different phenotypes.

Method

$CD14^+$-monocytes from healthy donors were cultured in the presence of M-CSF, IFN-γ, IL-4 or IL-10. Expression of the *PADI*2 and 4 mRNAs and proteins were measured by RT-qPCR and immunoblotting, respectively.

Results

Both mRNA and proteins encoded by *PADI*2 and 4 genes are expressed in human monocytes. In the various Mϕ subsets, *PADI*2 gene is more weakly expressed than in monocytes except for the IFN-γ Mϕ subset. By contrast, *PADI*4 gene expression is suppressed in all Mϕ subsets except for the IFN-γ Mϕ in which *PADI*4 mRNAs are weakly detected. Consistently with mRNA expression, PAD2 is expressed in all Mϕ subsets, mainly in the IFN-γ Mϕ whereas PAD4 is no longer detectable except for IFN-γ Mϕ.

Conclusion

PAD2 is expressed at various degrees in the four analysed Mϕ phenotypes but PAD4, only in the IFN-γ Mϕ. This reinforces the hypothesis of a role for monocytes and Mϕ in genesis of ACPA epitopes in the ST.

AUTO1-0960
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

IgG SUBCLASSES ALTERATIONS AND THEIR ASSOCIATION WITH AUTOIMMUNE DISEASES

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Background

It has been already described the correlation between certain immune-mediated disorders and elevated serum IgG4.However, no attention has been paid to other IgG subclasses. In this retrospective study, we measured the serum levels of IgG subclasses in several autoimmune diseases in order to find out a clinical association.

Method

Sera from 44 patients with Rheumatoid Arthritis (RA), 26 with Rapidly Progressive Glomerulonephritis (RPGN), 17 with Celiac Disease, 22 with Graves Disease (GD), 24 withHashimoto's Thyroiditis and 14 with Systemic Lupus Erythematosus (SLE) were analyzed by turbidimetry using SPAPLUS (The Binding Site, Birmingham, UK) in order to determine the proportion of the different IgG subclasses and total IgG concentration. As disease control group, 24 patients with hepatitis C virus (HCV) were included.

Results

Celiac disease presented a significant elevated percentage of IgG1; otherwise RPGN, RA, GD and SLE had an elevation in the percentage of IgG4 with not increased total IgG. Patients with HCV, Hashimoto´s Thyroiditis and SLE presented an elevated concentration of total IgG mainly due to an elevation in IgG1 in all of themexcept for HCV that had also elevated IgG4. It is remarkable, as well, the lower proportion of IgG2 in RPGN and Celiac Disease.

Conclusion

This study confirms that serum IgG subclass concentrations and percentages may be altered in patients with autoimmune diseases. The results confirm some established associations between increased IgG1 and patients withHCV and SLE. Another interesting fact could be a possible novel association between low total IgG and CD.However, further studies are needed.

AUTO1-0166
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

UNDISCLOSED CHANGE IN REAGENT KIT DETECTED BY A RELIABLE IN-HOUSE CONTROL

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Background

Many laboratories rely solely on kit controls for assay validation, thereby missing out on important information provided by an in-house control. We demonstrate the value of routinely analyzing an in-house control with every assay run.

Method

Over a period of two months a significant increase in the proportion of positive anti-actin samples was noticed. Simultaneously, a significant shift in in-house control, traced to a change in kit lots, was registered. However, kit controls remained stable. Therefore, blood samples from blood donors tested in relation to initial method validation and samples from an external quality assessment program, were reanalyzed.

Results

Using new kit lots mean concentration of in-house control were 52.9 AU, compared to 39.4 AU with old lots (Figure 1, p=1.17*10^{-16}). Correspondingly, the proportion of positive patient samples increased from 22% using old kit lots to 31% with new lots (p=0.0017). In 2011, the specificity was 97.5% compared to 80% in 2017 at a cut-off of 20 AU. Heightening cut-off to 35 AU gave an acceptable specificity of 92.5% (Figure 2). Reanalyzing external quality samples with new kit lots gave a higher error rate, from 20% to 50% (Table 1).

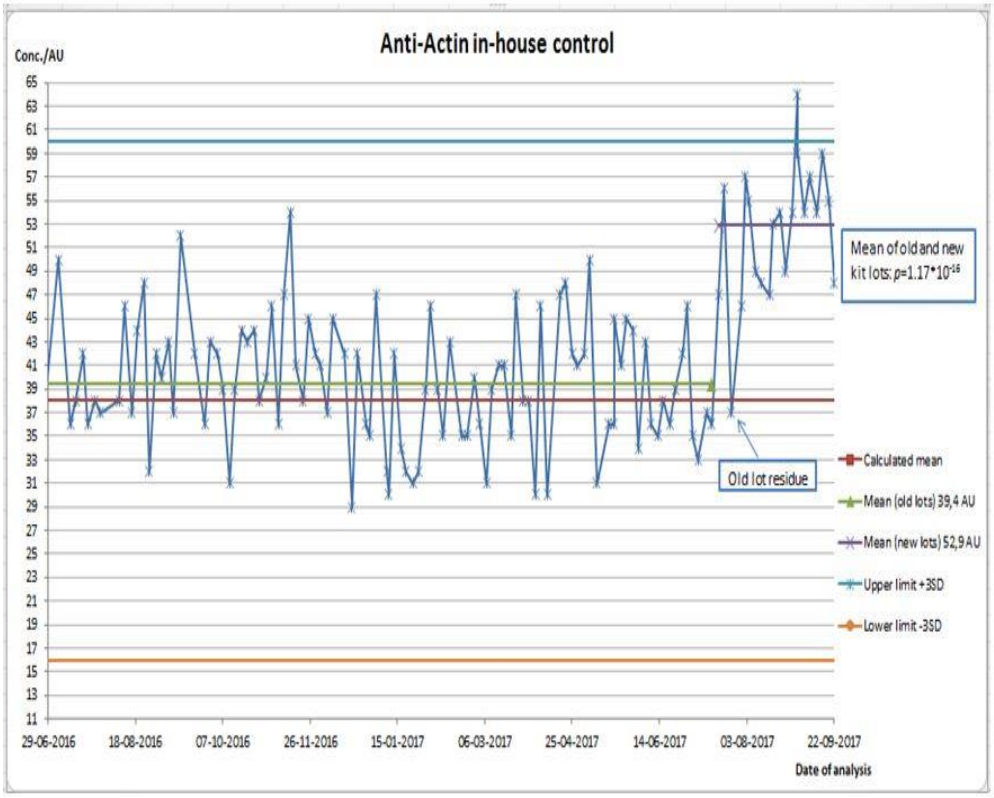
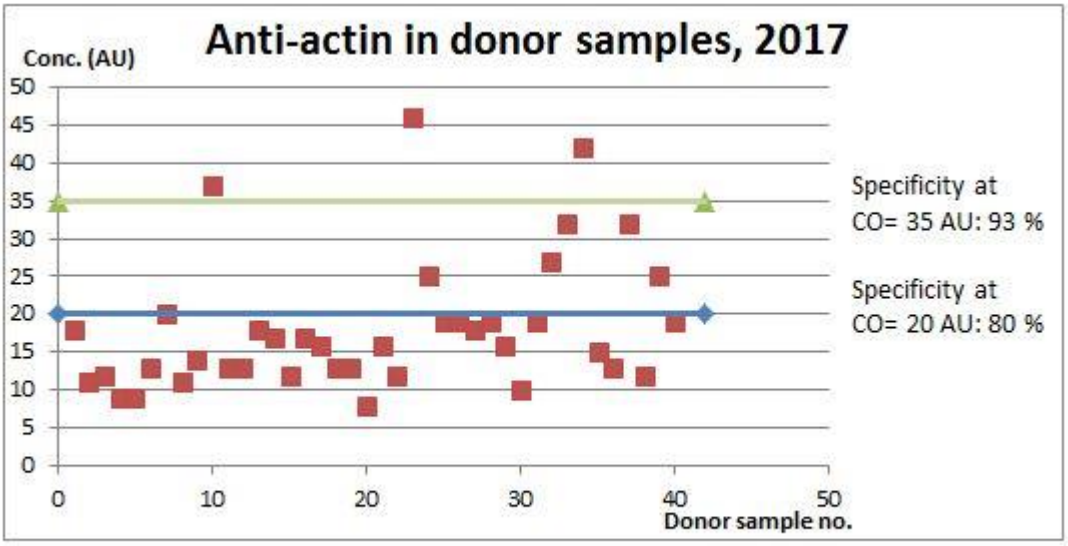


Figure 1: Throughout the illustrated period of time the same in-house control sample material has been analyzed with every assay run. The calculated mean and limits of acceptance are marked, as are the actual mean concentration for new and old lots respectively.



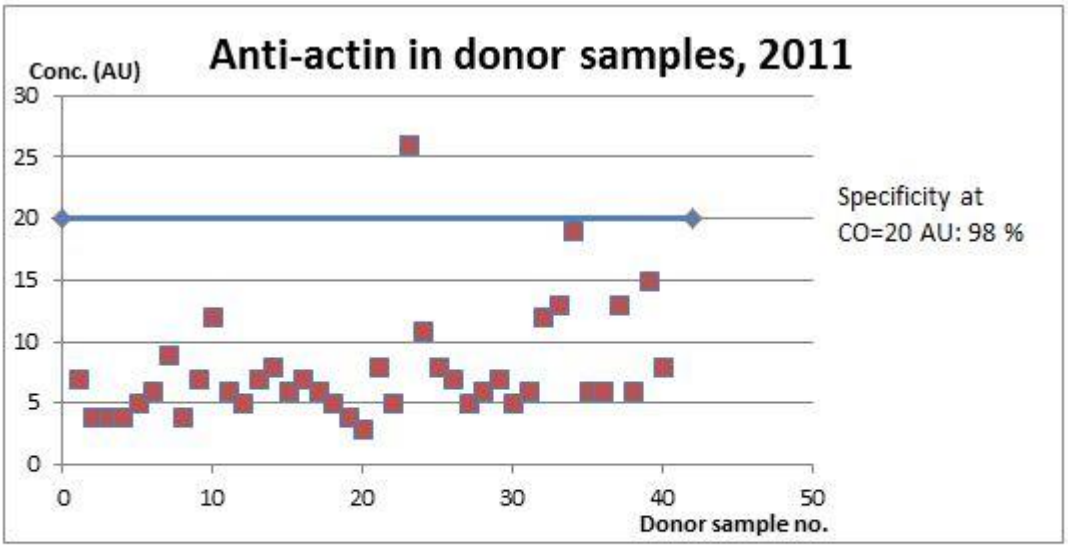


Figure 2: 40 healthy blood donor samples were analyzed in relation to method validation in 2011 and the cut-off=20 AU as stated by the manufacturer was confirmed. Reanalysis of these samples using new kit lots illustrates a significant shift and as a result a new cut-off=35 AU has been temporarily implemented.

Year of distribution	Specimen ID	Reported results (CO=20 AU)	Results Oct. 2017 (CO=20 AU)	Anti-actin target
2015	154-4	POS/22 *	POS/29 *	negative
2016	160315-2	NEG/8	NEG/13	negative
2016	160315-3	POS/27 *	POS/63 *	negative
2016	160920-1	NEG/11	POS/24 *	negative
2016	160920-3	NEG/18	POS/52 *	negative
2016	166-4	NEG/13	NEG/14	negative
2017	170321-1	NEG/11	NEG/16	negative
2017	170321-2	NEG/6	NEG/12	negative
2017	170321-3	NEG/13	POS/21 *	negative
2017	173-4	NEG/16	NEG/16	negative
	Error rate	**20%**	**50%**	

Table 1: Presentation of selected specimens from participation in EQA for anti-actin which has been reanalyzed using a new kit lot. At CO=20 AU the new kit lot shows a higher error rate from 20 % to 50 %.

Conclusion

Due to an in-house control a significant shift in the mean concentration following lot change was detected and handled in a timely manner, ensuring consistency when reporting results to clinicians. Consequently the manufacturer chose to adjust the reagent. Using in-house controls ensures reliable results for quantitative autoimmune analyses.

AUTO1-0953
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

PRACTICAL EXPERIENCE WITH AN ALTERNATIVE ANA ALGORITHM

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Objective:
To assess the current ANA algorithm with the goal of suggesting new methods of testing in order to cope with a major increase in workload in a maximum capacity situation. After deciding on an option, assess the effects on workflow, costs and clinical implications.

Patients and Method:
Data on more than 50 000 patients were analysed to determine the source of the referral, sample analysis workflow, follow-up ANA testing performed, the information provided to the clinicians and costings. A further audit was performed after two years of the new algorithm and looking at over 30 000 samples.

Results:

2015 to 2017	New algorithm (with EliA CTD Screen in first line)	Old algorithm (with IFA on HEp-2 in first line)
ANAS (ANA Screen)	30,000	33,800
ANA screen (+)	12% (n=3600)	15.3% (n=5171) (n=4590 for 30 000)
ENAS Total	12.5%	13.3%
ENAS (-)	71%	73%
ENAS (+)	29%	27%
dsDNA Total	11.5%	16.1%
dsDNA (-)	83%	84%
dsDNA (+)	17%	16%

Conclusion:
The change from ANA IIF screening to EliA CTD Screen was the right choice for this laboratory, because while no samples were missed, it was possible to absorb a 40% increase in workload by the existing staffing structure. Additionally, the detection of Ro52/Ro60 was improved (mostly missed by Hep-2 and even by Hep2000), the positivity rate of the follow-up tests was increased and costs could be reduced. Last but not least, the expertise of the staff on ANA IIF improved, because they had more time to looking at positives.

AUTO1-0285
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

ANTINUCLEAR ANTIBODIES (ANA) IN POST ALLOGENEIC STEM CELL TRANSPLANTATION (ASCT): OCCASIONAL FINDING OR IMPORTANT ROLE?

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Background

Cases of patients presenting with autoimmunity following allogenic stem cell transplantation (ASCT) are increasingly being reported.
Circulating autoantibodies suggest an ongoing immune response, difficult to differentiate from *de novo* autoimune disease (AD). While the presence of autoantibodies is well reported in these disorders, their role remains not clear after ASCT.

Method

Our work consisted on a retrospective study, between the period of 1st of October 2016 and the 30th of September 2017. The goal was to identify the patients submitted to an ASCT that showed the occurrence of Antinuclear Antibodies (ANA), and whether there was a pattern change after ASCT. We selected the patients from the Stem Cell Transplants Unit (SCTU) nursery or outpatient clinic that had a positive ANA pattern, by indirect immunofluorescence, and assessed the findings of which pattern, titration, evolution of the pattern over time, diagnosis, conditioning scheme, type of donor and clinical association.

Results

We identified 85 patients with ANA requests, made based on clinical findings. 25 had positive ANA pattern and only two had autoimmunity assessment before the transplant. 1734 days was the mean period to appearance of a positive ANA test. Positivity correlates with clinical symptoms.

Conclusion

We concluded despite the uncertainty owing to the lack of controlled data, patients at an increased risk for developing a new AD after HSCT should be identified. The discrimination between multisystemic AD and cronic graft versus host disease (cGVHD) is not easy. Prospective evaluation of incidence and type of autoantibodies is essential to optimize management of these patients.

AUTO1-0952
DIAGNOSTIC KITS FOR PRACTICAL APPLICATIONS

COMPARISON OF THE CLINICAL UTILITY IN THE DETECTION OF ANTI-NUCLEAR ANTIBODIES BETWEEN THE ELIA CTD SCREEN AND INDIRECT IMMUNOFLUORESCENCE ON HEP-2 CELLS

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Background/Objectives:
We compared the Elia CTD screen (ECS), a fluoroenzymeimmunoassay incorporating 17 recombinant human antinuclear antigens (ANA), with indirect immunofluorescence (IIF) on Hep-2 cells in order to determine the clinical utility of the ECS in additon to or without IIF.

Design/Method:
We examined 1708 consecutive serum samples submitted for ANA testing using the ECS and IIF in parallel. In case of a positive screen result, commercial quantitative fluoroenzymeimmunoassays and/or immunoblots were performed for antibody differentiation. The medical records were evaluated for systemic rheumatic disorders.

Results: Concordance between ECS and IIF (ECS-/IIF-, n=1216; ECS+/IIF+, n=128) was observed in 1344 samples (78.7%).ECS+/IIF- results were found in 37 samples (2.2%); the subsets were negative in 13, and positive in 24 cases showing 30 antibody specificities. Most frequently, Ro (n=10) and low-titer dsDNA (n=11), and infrequently Sm, U1RNP, Jo-1, histone, SCL-70 and La antibodies were found. ECS-/IIF+ tests were observed in 288 specimens (16.9%), with 14 identifiable antibody entities. Except from one Centromer-B antibody in a subject with limited scleroderma, 13 antibodies not included in the ECS antigen panel (histone, n=5; Pl-12, n=1; nucleosome, n=4; AMA, n=3) were identified using IIF.

Conclusions: The ECS represents a safe diagnostic tool for ANA screening. However, based on the fact that some antigens are not incorporated in the ECS panel, and some ANA can also be missed by IIF, sequential or parallel screening with ECS and IIF may be reasonable when the clinical suspicion for connective tissue disease is high.

AUTO1-0208
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

APPEARANCE OF FALSE NEGATIVE ANTI-DSDNA RESULTS USING CIA DURING LUPUS PATIENT'S ROUTINE FOLLOW-UP

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Background

The detection of anti-double stranded DNA (dsDNA) antibodies is pivotal in the diagnosis and the follow-up of systemic lupus (SLE) but enzyme-linked immunosorbent assay (ELISA) or parented tests yield some discrepancies with Crithidia Luciliae testing (CLIFT). We report the observation of false negative anti-dsDNA results using the chemiluminescence immunoassay (CIA) BIO-FLASH® (Inova Diagnostics) in SLE patients during their follow-up. We analyzed the possible interference leading to false negative anti-dsDNA testing. We examine the interest of an ELISA (QUANTA lite HA dsDNA ELISA (Inova)) to complete the lab tests for those peculiar patients

Method

The study was retrospective and included 154 samples (142 patients) divided in four groups: 26 in positive control group (anti-dsDNA positive with CIA and CLIFT), 25 in negative control group, 16 in the false negative group (CIA negative/CLIFT positive) and 87 in the false positive group (CIA positive/CLIFT negative).

Results

The concordance in the negative and positive control groups was respectively 88% and 62% with the ELISA test. In the false negative group 10/16 patients were positive in ELISA. In the false positive group, 74 ELISA tests were negative and 13 were positive (Table 1). False negative CIA testing was not due to a pro-zone effect and not associated to any interference with cryoglobulin, hypergammaglobulinemia, or complement. No association with specific treatment was observed (Table 2).

	ELISA positive	ELISA negative
CIA + / CLIFT+	16	10
CIA - / CLIFT-	3	22
CIA - / CLIFT+	10	6
CIA + / CLIFT-	13	74

Table 1 : Results (positive or negative) of QUANTA lite HA dsDNA ELISA

Sample	CL	Values CIA (UC/mL) cut off ≤35	Values ELISA (UI/mL) cut off ≤30	Gamma-globulin (g/L)	Values CIA (UC/mL) with EDTA Add (Complement interference)	Values CIA (UC/mL) dilution 1/10 (pro-zone effect?)	Clinical/Treatment
1	Weak positive	16	15	nt	14	<9,8	SLE / Mycophenolate mofetil, prednisone
2	Positive	19	208	nt	23	<9,8	SLE / desogestrel
3	Weak positive	23	51	14,8	27	<9,8	SLE / Cyclophosphamide
4	Weak positive	24	48	13,7	23	<9,8	SLE/acide mycophénolique, chlorure ambémonium, ésoméprazole, estradiol, progesterone
5	Positive	26	41	nt	20	<9,8	SLE/Mycophenolate mofetil, prednisone
6	Positive	19	16	8,5	nt	nt	SLE/Hydroxychloroquine, prednisolone, hydroxychlorquine
7	Weak positive	19	30	6,3	nt	nt	SLE/Hydroxychloroquine, prednisone, hydroxychlorquine
8	Weak positive	<10	37	12,9	nt	Nt	SLE/no treatment
9	Positive	27	22	5,0	21	<9,8	SLE/ RITUXIMAB, prednisone, methotrexate
10	Weak positive	29	33	13,8	30	<9,8	RA/Infliximab, methotrexate, prednisone
11	Positive	29	22	10,6	24	<9,8	SLE/ Hydroxychloroquine
12	Positive	34	89	7,7	35	<9,8	SLE/ Mycophenolate mofetil, prednisone
13	Positive	27	65	12	nt	nt	SLE/hydroxychloroquine, prednisone, amoxicilline/ac clavulanique
14	Positive	28	84	7,1	nt	nt	SLE /Mycophenolate mofetil, Prednisone
15	Positive	30	22	nt	nt	nt	SLE/Hydroxychloroquine
16	Weak positive	32	63	12	nt	nt	SLE/ Hydroxychloroquine

Table 2 : Characteristics of 16 samples (11 patients) in the false negative group (CIA -/ CL+)
P: positive, N : negative, NT: not tested; RA: Rheumatoid arthritis ; SLE : systemic lupus erythematosus

Conclusion

We report the appearance of false negative results by CIA in SLE patient's. We propose that ELISA testing could be useful, in a third step, to ensure proper quantitative follow-up of SLE patients.

AUTO1-0240
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

ORDERING PATTERNS OF ANTI-CCP, IGM RF AND ANA - A RETROSPECTIVE REGISTER-BASED POPULATION STUDY

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Background

The 2010 ACR-EULAR classification criteria for rheumatoid arthritis (RA) include both anti-cyclic citrullinated peptide (CCP) and rheumatoid factor (RF), but not anti-nuclear antibodies (ANA). However, these analyses are often ordered as a triad. We wanted to describe the ordering pattern, aiming to ensure a more appropriate future use of these analyses.

Method

A retrospective register-based population study (Funen County ~ 500.000 inhabitants). Data on ordering patterns and test results for IgM RF and anti-CCP with addition of concomitant ANA from 2006 to 2016 were described.

Results

There were a total of 165.394 orders, containing 358.252 test results (anti-CCP 116.624, IgM RF 155.114, concomitant ANA 86.514). Amount of tests analysed increased yearly and IgM RF was the preferred test (Figure 1). The triad of anti-CCP, IgM RF and ANA comprised 41% of orders. At the first test, 9% were anti-CCP positive and 13% were IgM RF positive. 90% had a repeated anti-CCP (range 2-30) and 66% had a repeated IgM RF (range 2-30). Overall positivity rates distributed on ordering unit are shown in Table 1.

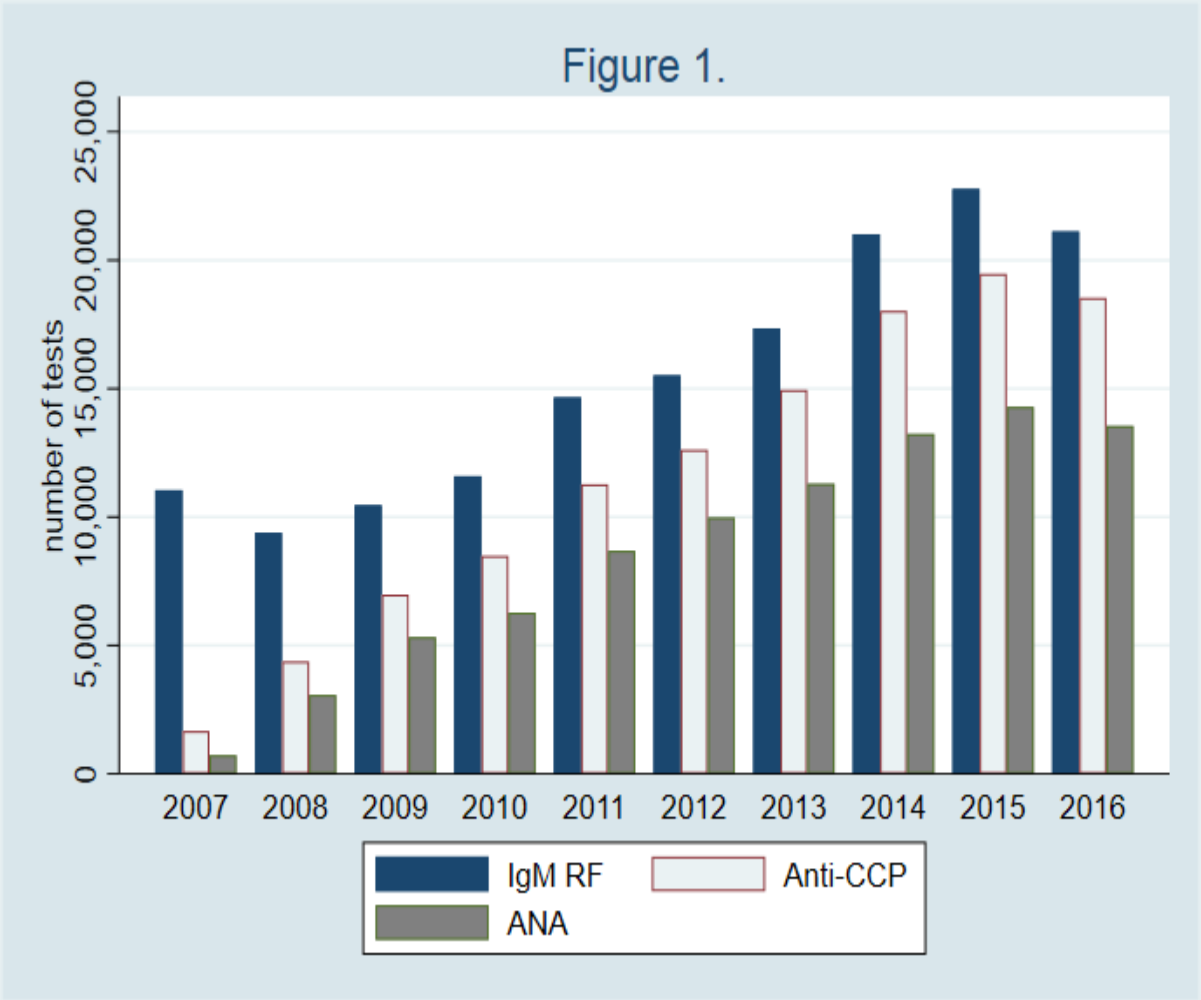

Table 1. Rate of positive test results

	Anti-CCP (%)	IgM RF (%)	ANA (%)
Primary care	5.3	13.2	11.9
Rheumatologic departments	15.1	24.3	17.2
Tertiary care*	10.5	19.5	13.6
Pediatric department	15.0	12.0	14.3

Al orders are included, also repeated orders.
*Orders from rheumatologic department excluded.

Conclusion

Anti-CCP is a specific serological marker for RA. Despite this, IgM RF has remained the preferred test during the last decade. There seems to be a tendency towards overuse, based upon repeated testing and low positivity rates. Forwardly the utility of these analyses will be evaluated by connecting our results to patient diagnosis.

AUTO1-0246
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

A STEP TOWARDS STANDARDIZATION: A METHOD FOR END-POINT TITER DETERMINATION BY FLUORESCENCE INDEX OF AN AUTOMATED MICROSCOPE.

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Background

Indirect Immunofluorescence (IIF) is widely considered the Gold Standard for Antinuclear Antibody (ANA) screening. However, the high inter-reader variability remains the major disadvantage associated with ANA testing and the main reason for the increasing demand of the computer-aided immunofluorescence microscope. Previous studies proposed the quantification of the fluorescence intensity as an alternative for the classical end-point titer evaluation. However, the different distribution of bright/dark light linked to the nature of the self-antigen and its location in the cells result in different mean fluorescence intensities. The aim of the present study was to correlate Fluorescence Index (F.I.) with end-point titers for each well-defined ANA pattern.

Method

Routine serum samples were screened for ANA testing on HEp-2000 cells using Immuno Concepts Image Navigator System, and positive samples were serially diluted to assign the end-point titer. A comparison between F.I. and end-point titers related to 10 different staining patterns was made.

Results

According to our analysis, good technical performance of F.I. (97% sensitivity and 94% specificity) was found. A significant correlation between quantitative reading of F.I. and end-point titer groups was observed using Spearman's test and regression analysis. A conversion scale of F.I. in end-point titers for each recognized ANA-pattern was obtained.

Conclusion

The Image Navigator offers the opportunity to improve worldwide harmonization of ANA test results. In particular, digital F.I. allows quantifying ANA titers by using just one sample dilution. It could represent a valuable support for the routine laboratory and an effective tool to reduce inter- and intra-laboratory variability.

AUTO1-0409
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

ANTI-RO60 SEROPOSITIVITY DETERMINES ANTI-RO52 EPITOPE MAPPING OUTCOME IN PATIENTS WITH AUTOIMMUNE RHEUMATIC DISEASES

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Background

We provide a comprehensive epitope recognition analysis of anti-Ro52 antibodies in patients with autoimmune rheumatic diseases (ARDs) and non-ARDs.

Method

Tests were performed in 147 anti-Ro52 positive patients with various autoimmune diseases (ARD), including 40 SjS, 28 SLE, 30 SSc 35 PBC and 14 with various ARDs. A specifically-designed line immunoassay containing five recombinant Ro52 fragments [Ro52-1 (aa 1-127), Ro52-2 (aa 125-268), Ro52-3 (aa 268-475), Ro52-4 (aa 57-180), and Ro52-5 (aa 181-320) was used.

Results

All patients reacted with Ro52-2 while reactivity to Ro52-3 was totally absent except of 6/40 (15%) SjS ($p<0.05$, for all). Reactivity to Ro52-1, Ro52-4 and Ro52-5 was found; in SjS 55%, 37.5% and 70%, respectively; in SLE in 53.6%, 57.1% and 64.3%, respectively; in SSc in 26.6%, 16.6% and 46.6%, respectively; in PBC in 5.7%, 2.9% and 42.9%. Epitope recognition patterns is similar in SLE and SjS but statistically differs between SjS and SSc (or PBC, $p<0.05$) and between SLE and SSc (or PBC, $p<0.05$), for at least one of Ro52-1, Ro52-3 or Ro52-5 epitopes. When epitope mapping was analysed according to anti-Ro60 (SS-A) reactivity, we noted that Ro52/Ro60 double-positive patients more frequently reacted with Ro-52-1 irrespectively of the disease state ($p<0.05$ for all diseases). Ro52/Ro60 double-positive patients reacted more frequently with Ro52-4 and Ro52-5 and differences were observed among specific ARDs.

Conclusion

All patients with anti-Ro52 antibodies recognize a common epitope (aa 125-268). Recognition of other dominant Ro-52 epitopes depends on concurrent anti-Ro60 reactivity.

AUTO1-0480
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

ISO 15189, TEST VALIDATION AND AUTOIMMUNITY TESTS, JOINT EFFORTS IN THE NETHERLANDS

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Background

In Europe the Standard ISO 15189:2012 “Medical Laboratories – Requirements for quality and competence” (ISO15189) has been adopted as accreditation standard for the medical laboratories. ISO 15189:2012 requires validation of methods used in the medical laboratory, and list a series of performance parameters to include. Although these performance parameters are feasible for clinical chemistry analytes, application in the validation of autoimmunity tests is a challenge. Lack of gold standards or reference methods in combination with the scarcity of well defined diagnostic samples of patients with rare diseases make validation of new assays difficult.

Therefore Dutch medical immunology laboratory specialists combined efforts regarding validation of autoimmune tests. Improvement of the quality of the studies, sufficing ISO standards, was the goal of this initiative in combination with reduction of the individual efforts made to introduce new autoimmune tests. Sharing the validation data and reports enables the individual laboratory to perform only a method verification, which is a more achievable goal.

Method

We developed a phased plan of multicenter validation studies, for which we requested eligible autoimmune tests to be validated and for participants to perform the validation studies.

Results

Two studies have been completed (anti-Scl70, anti-TSH-receptor) and the results have been shared with interested Dutch laboratory specialists. Two more studies are being conducted (anti-intrinsic factor, calprotectin).

Conclusion

Evaluation of the first two studies shows that both goals – improvement of the quality of validation and reducing individual workload- are met. Especially the clinical performance

characteristics like sensitivity and specificity are more robustly tested in multicenter studies.

AUTO1-0648
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

VARIABILITY IN METHOD OF TESTING FOR ANTINUCLEAR ANTIBODIES (ANA): A SURVEY OF PARTICIPANTS IN THE COLLEGE OF AMERICAN PATHOLOGIST'S (CAP) PROFICIENCY TESTING PROGRAM

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Background

A 2010 American College of Rheumatology position paper designated

indirect immunofluorescence assay (IFA) on HEp-2 cells the "gold standard" for ANA testing and

that laboratories performing other methods should state the method used and describe its

performance parameters. This study was performed to determine laboratory practices in ANA

testing.**Method**

Laboratories participating in CAP proficiency testing for ANA answered supplemental

questions in 2016. Of 5847 kits distributed, 1206 (21%) participants responded (942 in the US

and 264 international).**Results**

ANA screening method varied: 56% IFA, 21% ELISA, 12% multi-bead immunoassay, and

18% "other" methods. Ordering test name indicated method used in only 32%; only 39% stated

method used on the report. Of 644 laboratories, 80% used HEp-2 substrate, 18% HEp-2000

(HEp-2 cell line engineered to overexpress SSA), and 2% "other." Slides were prepared manually

(67%) or on an automated platform (33%), and examined by direct microscopy (84%) or images

captured by an automated platform (16%). IFA patterns were interpreted by personnel in 95% of

laboratories; <1% used automated image capture and analysis solely; 4% interpreted images both

by personnel and an automated platform. 97% of 641 laboratories reporting ANA by IFA provided

a titer. Only 51% reported a positive result at the traditional 1:40 dilution. Titer was reported to

endpoint routinely by 43%, only upon request by 23%, or never by 35%. 8% did not report dual

patterns. Of those reporting multiple patterns, 24% did not report a titer with each pattern.**Conclusion**

Only slightly more than half of testing laboratories utilize the ACR “gold standard”

IFA method with HEp-2 cell substrate.

AUTO1-0305
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

EVALUATION OF A NOVEL MULTI-ANALYTE ASSAY FOR THE DETECTION OF AUTOANTIBODIES AS AN AID IN THE DIAGNOSIS OF ANTIPHOSPHOLIPID SYNDROME (APS)

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Background

Antibodies to antiphospholids (aPL) and associated proteins are a hallmark in the diagnosis of antiphospholipid syndrome (APS). Recently, a novel fully automated bead based system has been developed which allows for the detection of autoantibodies to cardiolipin (aCL) and beta 2 glycoprotein I (β2GPI). This study aimed to analyze the clinical performance of the novel system and compare to reference methods using clinically characterized samples.

Method

A total of 279 samples were collected from APS patients and various other disease controls (n=228) and were tested for aCL and anti-β2GP1 antibodies. Antigens were coupled to paramagnetic particles and tested using a novel fully automated bead based immunoassay (research use only). A reduced number were also tested by reference methods for comparison studies. Clinical sensitivity and specificity was calculated for aCL and β2GP1 IgG, IgM and IgA isotypes and comparative analysis were performed on the predicate device.

Results

The sensitivity and specificity for the novel aCL and β2GP1 assays are outlined in the table below.

The correlation between platforms was good for both aCL and β2GP1 assay for all isotypes.

	aCL IgG	B2GP1 IgG	aCL IgA	B2GP1 IgA	aCL IgM	B2GP1 IgM
Sensitivity (95% CI)	67.0% (61.3-2.3%)	41.6% (35.9-7.4%)	43.4% (37.7-49.2%)	38.4% (32.8-44.2%)	22.9% (18.4-28.2%)	21.5% (17.1-26.7%)
Specificity (95% CI)	90.8% (96.3-93.9%)	97.4% (94.4-8.8%)	98.2% (95.6-99.3%)	97.4% (94.4-98.8%)	97.8% (95.0-99.1%)	98.2% (95.6-99.3%)
LR+	7.3	15.8	24.7	14.6	10.5	12.3
LR-	0.36	0.60	0.58	0.63	0.79	0.80
Odds ratio (95% CI)	20.0 (12.0-33.4)	26.3 (11.5-60.0)	42.9 (16.1-114.1)	23.0 (10.1-52.5)	13.3 (5.4-32.7)	15.3 (5.7-41.3)
Youden's index	0.58	0.39	0.42	0.36	0.21	0.98

Conclusion

Our data shows excellent analytical and clinical performance of the new autoantibody system for the detection of antibodies as an aid in the diagnosis of APS.

AUTO1-0344
DILEMMAS IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES, DETECTION AND STANDARDIZATION

ANA-IIF AUTOMATION: MOVING TOWARDS HARMONIZATION? RESULTS OF THE 2017 BELGIAN MULTICENTER STUDY.

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Background

Our study aimed to investigate whether the introduction of automated anti-nuclear antibody indirect immunofluorescence (ANA-IIF) analysis decreases interlaboratory variability of ANA-IIF titer results.

Method

26 of 31 (83.9%) Belgian laboratories that routinely use automated ANA-IIF participated. Table 1 gives an overview of the instruments used as well as the substrate, conjugates, and dilutions. Three serum samples (1/320 homogeneous; 1/80 fine speckled; negative) were analyzed by automated systems for intra-run and inter-run imprecision (CV) and endpoint titer by serial dilution. Besides, 2 of the 3 serum samples were distributed as an EQA sample to all Belgian laboratories performing IIF analysis, allowing comparison between manual and automated ANA-IIF analysis for each manufacturer.

Results

For some instruments (e.g. Novaview) a similar substrate, conjugate and screening dilution was used among all users, whereas for other instruments (e.g. G. Sight) different substrates were among users (**Table 1**).

Table 1. Overview materials and methods used by the participating laboratories

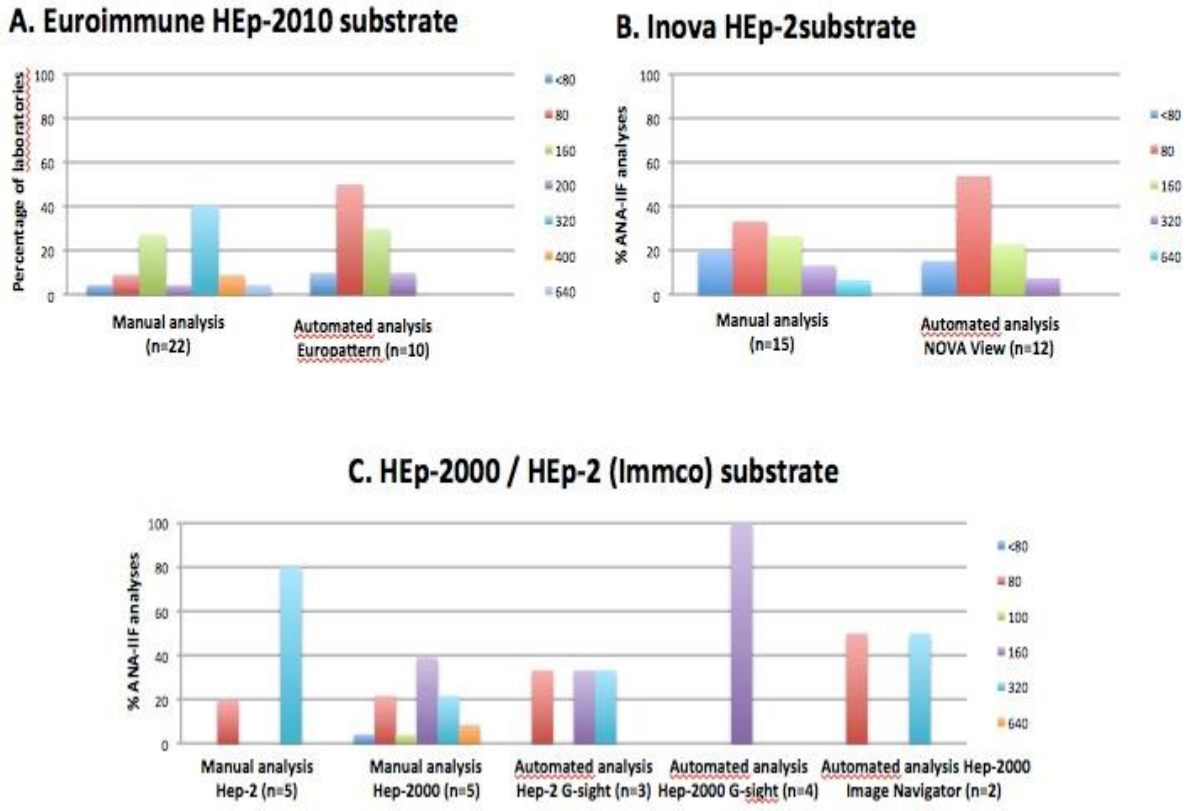
Company	Microscope	n	Substrate	Conjugate	Dilution	Pipetting robot
Inova	NOVA View	11	HEp2	IgG HCS	1/80	QUANTA-Lyser 2 (n=7) QUANTA-Lyser 160 (n=3) QUANTA-Lyser 240 (n=1)
Euroimmun	Europattern	6	HEp2010	IgG HCS (n=2) IgG HLCS (n=4)	1/80	PhD (n=2) Sprinter (n=3) Zenit UP (n=1)
Menarini	G-Sight	7	HEp-2 (n=3) HEp-2000 (n=4)	IgG HLCS (n=4) IgG HCS (n=3)	1/80 (n=6) 1/40 (n=1)	Zenit UP (n=4) Zenit S (n=2) Zenit SP (n=1)
Immunoconcepts	Image Navigator	2	HEp2000	IgG HCS	1/80	Beeline (n=1) Helmed (n=1)
Total		26				

IgG HCS = IgG heavy chain specific; IgG HLCS = IgG heavy and light chain specific

The variation of the reported IIF titer between laboratories was higher for manual analysis than for automated analysis. This was observed for all tested automated IIF systems

(**Figure 1**). However, despite the improved overall variation, significant differences in fluorescence intensity (> +/- 1 titer) were observed between instruments from the same manufacturer and between instruments from different manufacturers.

Figure 1. End point titer of IIF analysis of an EQA sample analyzed by manual or automated IIF. The figure shows the distribution of the end point titers (by serial dilution) reported by Belgian laboratories using either manual or automated IIF analysis.



Conclusion

The introduction of automated ANA-IIF analysis allows for more harmonized ANA-IIF result reporting. However, despite automation variation remains, and initiatives are needed to further standardize digitalized IIF analysis.

AUTO1-1084
EASI SESSION: MARKERS IN INFLAMMATORY MYOSITIS

IMMUNE MEDIATED NECROTIZING MYOPATHY: A MYOSITIS SPECIFIC ANTIBODIES-BASED ENTITY

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Myositis are an heterogenous group of auto-immune muscle diseases. They are characterized by a break of immunological tolerance to muscle leading muscle an impairment. They are either muscle specific auto-immune diseases or non-organ specific auto-immune diseases attested by the frequent extra-muscular manifestations such as skin changes, rheumatological and/or pulmonary involvement, the later exposing the patients to life-threatening complications.
Based on the clinical phenotype and the myopathological changes, the myositis were until recently categorized into two categories: polymyositis and dermatomyositis. Whereas this classification is still largely used it does not reflect the large spectrum of the myositis.
Since the 1976, the identification of the first myositis auto-antibody (Ab), fourteen other Ab have been described so far. In 1986, the anti-signal recognition particle (SRP) Ab has been specifically associated with polymyositis. Nevertheless, in 2002 a careful analysis of the myopathological features showed that 'anti-SRP+ polymyositis' was characterized by predominant muscle fibre necrosis whereas the lymphocytic inflammation was mild or absent. In addition, those patients did not have any extra-muscular manifestation. One year later, the new group immune mediated necrotizing myopathies (IMNM) was defined based on pathological criteria and isolated from PM.
In 2011, among a group of anti-SRP- IMNM, a new myositis specific Ab was isolated : anti-Hydroxy-Methylglutaryl-CoA Reductase (HGMCR). The phenotype of anti-HMGCR+ patients is close to those of the anti-SRP+ patients but anti-HMGCR+ patients are frequently statin-exposed.
To date, it appears that IMNM are muscle specific auto-immune diseases. They are the most severe myositis attested by the intensity of the muscle weakness and the poor out-come related to the importance of the muscle damages and the long disease duration. The pathophysiology has been partly clarified. The key role of auto-Ab in muscle injuries and in the muscle regeneration impairment open new therapeutic avenues.

AUTO1-1085
EASI SESSION: MARKERS IN INFLAMMATORY MYOSITIS

OVERVIEW ON ANTIBODIES IN INFLAMMATORY MYOSITIS AND RESULTS FROM A BELGIAN STUDY

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The interest in myositis-specific autoantibodies is growing. The recent EULAR/ACR classification criteria for idiopathic inflammatory myopathies include anti-jo-1 antibodies (Lundberg et al. Ann Rheum Dis. 2017;76:1955-1964) and new clinico-serological classifications of myositis have been proposed (Senécal et al. Arthritis Rheumatol. 2017;69:878-884). Distinct antibodies indeed define subgroups of disease. Antibodies to synthetases (e.g. Jo-1, PL-7, PL-12) define the anti-synthetase syndrome. Anti-TIF-1γ and anti-NXP-2 define a subgroup of dermatomyositis and are associated with malignancy in adults. Anti-MDA-5 antibodies are associated with myositis with overlap features such as interstitial lung disease and with amyopathic dermatomyositis. Anti-Mi-2 antibodies are associated with dermatomyositis. Anti-SRP and anti-HMGCR are associated with necrotizing autoimmune myositis. At present, easy to use commercial line/dot immunoassays are available for determination of myositis-specific antibodies.

AUTO1-1079
EASI SESSION: MARKERS IN INFLAMMATORY MYOSITIS

THE USE OF MYOSITIS SPECIFIC ANTIBODIES IN DAILY CLINICAL PRACTICE

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Background:
Traditionally, the diagnosis of idiopathic inflammatory myopathies (IIM) is based on clinical findings, muscle enzyme levels, electromyography and biopsy. Newer approaches include the detection of myositis-specific autoantibodies (MSA), with MSA identified in about 50% of patients.
Today, several commercial platforms for MSA detection have become commercially available. The aim of this study was to document the frequency of MSA as detected by 2 lineblots (LB) in a set of consecutive patients for which MSA were requested and to correlate the MSA results with the origin of the request, the clinical diagnosis and other laboratory findings.

Material and methods:
A total of 118 consecutive routine samples for which MSA were requested, was analysed on indirect immunofluorescence (IIF HEp-2 [Menarini]) and 2 lineblots (MYO12 blot [D-Tek] and EUROLine Autoimmune inflammatory myopathies 16 Ag [AIM16, Euroimmun]). All patients were retrospectively categorized by the treating medical specialist as IIM (20 definite, 11 probable), immune mediated inflammatory disease (IMID) - myositis overlap not excluded (n=29), myopathic features without IIM (n=1), IIM excluded (n=46), and lost from follow-up/no data available (n=11). In addition all laboratory test were also performed on a set of 107 controls [50 systemic sclerosis (SSc), 29 systemic lupus erythematosus (SLE) and 28 rheumatoid arthritis patients (RA)]).

Results:

In total, 26% of patients were categorized as IIM (definite or probable), with most requests originating from the rheumatology (58%) and neurology departments (19%). MSA were detected in 17 (55%) of these IIM patients, with the highest frequencies observed for anti-HMGCR (13%, n=4), anti-Mi-2 (13%, n=4), anti-Jo1 (10%, n=3) and anti-TIFɣ (6%, n=2). Lower frequencies were found for anti-EJ, anti-NXP2, anti-MDA5 and anti-SAE (all 3%). Remarkably, 47% of MSA detected in IIM patients were only observed in 1 LB system, only half of them explainable by differences in the antigens present (missing of anti-HMGCR on Euroimmun). Nevertheless, all these patients had a MSA-compatible clinical IIM subtype.
In contrast, MSA were also observed in 12 patients with no convincing clinical diagnosis of IIM or myositis overlap syndrome (anti-TIFɣ in 6 [3 SSc,1 SLE, 1 RA and 1 IIM excluded]; anti-SRP in 1 [RA]; anti-SAE in 3 [1 SSc, 1 RA and 1 IIM excluded]; anti-Mi2 in 1 [SLE]; anti-Jo1 in 1 [IIM excluded]); all showing reactivity in only 1 LB system. Low antibody positivity was significantly more detected in non-IIM vs. IIM (77% vs.12%, p=0.0013). Moreover, less than 50% of the MSA in non-IIM patients showed a compatible

IIF pattern. Six other, mostly low positive, MSA (2 anti-SRP, 1 anti-PL7, 1 anti-TIFɣ, 1 anti-Jo1 and 1 anti-Mi2) were also detected in patients with non-conclusive autoimmune features (IIM could not be confirmed nor excluded).

Conclusion:

- LB may be an interesting tool to increase MSA detection within the former 'seronegative' IIM subgroup, allowing the identification of clinical subtypes.
- When applied in a context low to moderate clinical suspicion of IIM, the clinical importance of low positive MSA is currently unknown.
- The complexity of this clinical dilemma is additionally increased by the apparent specificity issues for certain antibodies.
- Constructive interaction between laboratory experts and clinicians may contribute in overcoming these difficulties.

AUTO1-1076
EASI SESSION: MARKERS IN INFLAMMATORY MYOSITIS

FREQUENCY AND CLINICAL ASSOCIATION OF MYOSITIS ANTIBODIES IN THE NETHERLANDS: A ONE-YEAR SURVEY OF ALL DUTCH PATIENTS

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Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of connective tissue diseases, collectively known as myositis. In time recognition of an IIM is of importance considering the (severe) long-term clinical complications. With the EULAR/ACR classification criteria (2017) considerable advancement has been made in the diagnostic workup of IIM. These criteria take into account clinical parameters as well as laboratory measurements, such as Jo-1 autoantibody positivity.

However, several additional autoantibodies are known. These can be classified into myositis specific antibodies (MSA) and myositis associated antibodies (MAA). As individual antibodies occur at low frequency, the development of line-blots allowing multiplex antibody analysis has improved the laboratory diagnostic confirmation of IIM. The Euroline myositis line-blot assay (Euroimmun) allows screening for 15 MSA/MAA, i.e. Ku, SRP, EJ, OJ, Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, PL-12, PL-7, Jo-1, PM/Scl-75 and PM/Scl-100. In addition, an ELISA (INOVA) is available for antibodies to HMGCR.

To evaluate the clinical significance of detection and intensity quantitation of MSA/MAA in the Netherlands, we performed a retrospective analysis of all Dutch requests for extended myositis screening within a 1 year period.

We will present preliminary data from 700 patients regarding [1] frequency and specificity of MSA/MAA detection and [2] antibody reactivity in relation to IIM and its complications. Our data will help to incorporate/establish the role of autoantibody detection in clinical guidelines, facilitating improved diagnosis, treatment and prognosis of IIM.

AUTO1-0906
EASI SESSION: MARKERS IN INFLAMMATORY MYOSITIS

THE DIAGNOSTIC VALUE OF ANTI-HMGCR ANTIBODIES IN THE IMMUNE MEDIATED NECROTIZING MYOPATHY FOLLOWING STATIN EXPOSURE.

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Background
Anti-HMGCR antibodies represent a characteristic serological feature of statin associated immune-mediated necrotizing myopathy (IMNM). We assessed the prevalence of anti-HMGCR antibodies in patients with suspected IMNM following statin exposure and patients with other autoimmune rheumatic diseases.
Materials and methods
We evaluated the presence of anti-HMGCR autoantibodies in sera samples from 26 statin-exposed patients who were suspected of having IMNM, 38 patients with different inflammatory and autoimmune rheumatic diseases and 29 healthy subjects. The autoantibodies were evaluated by a novel chemiluminescence QUANTA Flash HMGCR kit utilizing BIO-FLASH system. Additional assessment of sera from the control groups and from 13 patients with suspicion for IMNM was performed using the QUANTA Lite® HMGCR ELISA kit.
Results
All of the patients from the statin-exposed group were positive for anti-HMGCR when evaluated by CIA. 12 sera from patients in this group were determined positive for anti-HMGCR antibodies by both assays. Only one of the 13 samples that were found to be positive by ELISA was negative by CIA. A very good qualitative correlation ($\kappa = 0.95$; 95 % CI 0.85-1.0) and quantitative agreement (Spearman's rho 0.87; P value < 0.0001; 95 % CI 0.62-0.96) were found between these two assays. All samples from healthy subjects and from the disease-controlled patient cohort were negative for anti-HMGCR antibodies, as determined by both assays. In comparison with ELISA, the CIA assay exhibited high sensitivity and specificity values of 92.3 and 100 %, respectively. Receiver operating characteristic analysis for CIA and ELISA yielded area under the curve values of 0.99.
Conclusion
The presence of anti-HMGCR antibodies may be a useful biomarker of IMNM in statin-exposed patients. There is a good correlation between the two anti-HMGCR antibody assays evaluated in the present study.

AUTO1-1080
EASI SESSION: MARKERS IN INFLAMMATORY MYOSITIS

USING FLUOROENZYMEIMMUNOASSAY FOR ANTI-SRP ANTIBODIES IN CHINESE PATIENTS WITH INFLAMMATORY MYOSITIS

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Anti-Signal Recognition Particle (SRP) antibody is one of the many myositis specific antibodies with unique clinical presentation and patients with anti-SRP can have severe weakness and cardiac involvement. Immunoprecipitation method to detect anti-SRP is the gold standard for patients with inflammatory myositis. Yet immunoprecipitation method is time consuming and technique-dependent and is not available in every medical center. Anti-Jo-1 and anti-Mi-2 using fluoroenzymeimmunoassay method had proven to be effective in clinical practice, which is commercially available.
We aimed to find patients with anti-SRP in patients with myositis using fluoroenzymeimmunoassay and compared with their clinical manifestations.

AUTO1-0423
ENDOCRINOLOGY AND THYROID AUTOIMMUNITY

IMPLICATION OF MIRS 199A-3P/5P IN OXIDATIVE STRESS AND ANGIOGENESIS IN LOCAL AND SYSTEMIC EFFECTS OF A TH2 AUTOIMMUNE DISEASE: GRAVES' THYROIDITIS.

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Background

Graves' thyroiditis (GD) is characterized by hyperthyroidism and often associated to ophthalmopathy (TAO). GD thyroids and adipose tissue present high oxidative stress (OS) and hypervascularization. miR199a-3p (3p) and miR199a-5p (5p) are involved in endothelial function, OS, angiogenesis and adipogenesis. Therefore, we aimed to measure 3p/5p expression in samples from GD patients and evaluate their potential impact on development of GD-clinical and systemic effects.

Method

Thyroid samples were obtained from patients operated for multinodular goiters (controls) or GD, orbital fat samples came from blepharoplasty or TAO. miRs expressions were evaluated following Maxwell extraction and quantitative real-time PCR. To mimic GD, human primary thyrocytes were stimulated with IL-4. Microvascular endothelial cells were cultured in matrigel support in the presence of medium from non-treated or IL-4 treated (GD-conditioned medium) thyrocytes and angiogenic effect of GD was evaluated by tubes formation. Proteins have been analyzed by immunohistochemistry and Western Blot.

Results

GD thyrocytes showed an increased 4-hydroxynonenal, indicating a rise in lipid peroxidation, and increased catalase expression suggesting improved H_2O_2 detoxification. NADPH-oxidase-4 upregulation in GD thyroids correlated with HIF-1α stabilisation and upregulation of VEGF expression. GD-conditioned medium promoted tubes formation in 2D-endothelial cultures. A significant reduction of 3p/5p expression in GD thyroids was observed. Interestingly, GD orbital adipocytes also showed a downregulation of 3p/5p.

Conclusion

In conclusion, we showed a dramatic reduction in miR199a-3p/5p expression in GD-thyroid extracts and GD-orbital fat. Taken together, our results are in agreement with a potential implication of these miRs as regulators of OS, angiogenesis and the systemic manifestations of GD.

AUTO1-0070
ENDOCRINOLOGY AND THYROID AUTOIMMUNITY

PATIENTS WITH HASHIMOTO THYROIDITIS PLUS PERIODONTITIS HAVE A MORE FREQUENT DESTRUCTION OF HYALURONIC ACID AND MEDICAL HISTORY OF ADENOCARCINOMA

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Background

Hashimoto thyroiditis (HT) and Periodontitis (PO) are frequently associated auto-immune diseases. We investigated whether patients with HT plus PO are at increased risk of destruction of HA and of adenocarcinoma. We also investigated whether chronic herpetic infections or reflux of biliary salts may favor PO.

Method

All patients consulting a private gastroenterologist and presenting with PO or HT were prospectively enrolled into a 12-months cohort study. 95 patients with neither HT nor PO were also prospectively enrolled.

Saliva was collected with swabs. PCR was run for Herpes simplex 1/2 and CMV (Amplix® from Alldiag®; reagents: Bioneer® and Adiavet®) in a central laboratory.

All patients underwent an abdominal ultrasound to look for jejunoduodenal reflux (JDR). A dosage of plasmatic HA was also performed.

Results

28 patients with HT plus PO were enrolled; 42 patients with HT only and 33 patients with PO only. HA plasmatic levels were higher in patients with HT+PO ($p<0.001$), as well as the percentage of RJD ($p<0.001$), HSV1/2 ($p<0.001$) or CMV ($p<0.05$) infections, or adenocarcinoma ($p<0.001$) in comparison to the control-group. See table.

Diseases (number of patients)	Hyaluronic acid	Jejunoduodenal reflux (JDR)	JDR+HSV	HSV1/2	CMV	Adenocarcinoma (number of cases)
HT+PO (28)	66.7 +/- 46.8§ p<0.05	71.3%* P<0.001	57.1%* P<0.001	71.4%* P<0.001	17.8%§ p<0.05	17.9% (5)* P<0.001
PO without HT (33)	41.8 +/- 23.0	81.8%	63.6%	66.7%	15.2%	6.1% (2)
HT without PO (42)	42.8 +/- 23.1	33.3%	16.7%	50%	16.7%	7.1% (3)
Neither HT nor PO (95)	45.1 +/-24.9§	26.3%*	4.2%*	18.9%*	11.6%§	2.1% (2)*

Conclusion

Plasmatic HA levels are elevated only when HT is associated with PO. The risk of AC is particularly high in patients with HT+PO and high levels of HA. Physician should not forget to look for PO when they diagnose HT and consider this association as a sign of severe tissue destruction.

AUTO1-0297
ENDOCRINOLOGY AND THYROID AUTOIMMUNITY

THE PARAMOUNT ROLE OF CYTOKINES AND CHEMOKINES IN PAPILLARY THYROID CANCER

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Background

Chemokines play a paramount role in tumor progression, angiogenesis and metastasis. In papillary thyroid carcinoma (PTC), *RET/PTC* rearrangements and *BRAF* or *RAS* mutations activate a common transcriptional program in thyrocytes, including upregulation of the (C-X-C motif) ligand (CXCL)10 chemokine, stimulating proliferation and invasion. PPARγ is present in thyroid tissue, and treating thyrocytes with PPARγ activators, at near-therapeutical doses, IFNγ-stimulated CXCL10, CXCL9 and CXCL11 secretion was significantly inhibited.

Method

CXCL9 and CXCL11 were measured basally and after 24 h of stimulation with IFNγ and/or TNFα in presence/absence of PPARγ agonists. Moreover, PPARγ knocking down was performed by RNA interference technique in PTC. Proliferation and migration were evaluated in PTC cells after PPARγ agonists, or CXCL9 or CXCL11 treatment.

Results

We demonstrate that CXCL9 and CXCL11 were absent basally in non-neoplastic thyroid cells (TFC) and PTC cells. IFNγ induced chemokines secretion in TFC, and PTC, while TNFα induced it only in PTC. IFNγ+TNFα induced a synergistic chemokines release in PTC, and at a lower level in TFC. PPARγ agonists suppressed dose-dependently IFNγ+TNFα-induced chemokines release in TFC, while stimulated it in PTC. PPARγ knocking down abolished the effect of PPARγ agonists on chemokines release. In PTC PPARγ agonists reduced proliferation, and CXCL9 or CXCL11 (100 and 500 pg/mL) reduced proliferation and migration ($P<0.01$).

Conclusion

We have shown a paramount role of cytokines and chemokines in PTC cells: a) IFNγ+TNFα induced a marked release of CXCL9 and CXCL11; b) PPARγ agonists stimulated CXCL9 and CXCL11 secretion, while inhibited proliferation; c) CXCL9 and CXCL11 inhibited proliferation and migration.

AUTO1-0296
ENDOCRINOLOGY AND THYROID AUTOIMMUNITY

DIFFERENTIAL MODULATION OF CXCL8 VERSUS CXCL10, BY CYTOKINES, PPARγ, OR PPARα AGONISTS, IN PRIMARY CELLS FROM GRAVES' DISEASE AND OPHTHALMOPATHY

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Background

Thyrocytes secrete C-X-C chemokines, particularly (C-X-C motif) ligand (CXCL)8 and CXCL10, even if its physiopathological significance remains unclear. This study investigates the modulation of CXCL8 secretion *versus* CXCL10, in human thyroid follicular cells (TFC) in Graves' disease (GD), and in primary fibroblasts (OF) or preadipocytes (OP) from Graves' ophthalmopathy (GO).

Method

Cells were initially incubated with TNFα (1, 5, 10 ng/mL). Then, CXCL8 and CXCL10 were measured in supernatants of TFC, OF or OP cells basally and after 24h stimulation with IFNγ (1000 IU/mL) and/or TNFα (10 ng/mL), in presence/absence of different concentrations of PPARγ (0, 0.1, 1.0, 5, 10, 20 μM; pioglitazone), or PPARα agonist (5, 10, 50, 100 μM; fenofibrate).

Results

CXCL8, not CXCL10, was detected in basal conditions in TFC, OF and OP. CXCL8 secretion increased dose-dependently with increasing concentrations of TNFα. CXCL10 secretion was significantly induced by IFNγ ($P<0.01$) and not by TNFα, whereas CXCL8 was induced by TNFα ($P<0.01$), and inhibited by IFNγ ($P<0.01$) in TFC, OF and OP. The combination of TNFα and IFNγ synergistically increased the IFNγ-induced CXCL10 secretion ($P<0.01$) and reversed the TNFα-induced CXCL8 secretion ($P<0.01$), in TFC, OF and OP; pioglitazone had no significant effect on the secretion of CXCL8 stimulated by TNFα, while inhibited CXCL10. The PPARα agonist fenofibrate significantly inhibited both CXCL8, and CXCL10.

Conclusion

In conclusion, these results first show that TFC, OF, and OP secrete CXCL8 and CXCL10 differentially, stimulated by specific proinflammatory cytokines or their combination, finally determining the nature of infiltrating lymphocytes in human GD and GO.

AUTO1-0549
ENDOCRINOLOGY AND THYROID AUTOIMMUNITY

MACRO TSH: A THREE-YEAR REVISED EXPERIENCE OF A CLINICAL DIAGNOSIS LABORATORY IN PORTUGAL

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Background

During the last four decades, there has been considerable advances in the efficacy and precision of serum thyroid function testing. The development of the third and fourth generation assays for the measurement of serum thyroid stimulating hormone (TSH, thyrotropin) and the log-linear relationship with free thyroxine (T4), established TSH as the hallmark of thyroid function testing.

Method

The authors propose to present a 3-year revised experience of macromolecules interferences study in a clinical diagnosis laboratory in Portugal.

Results

We performed a literature review and found a very few small casuistic documented over the last 10 years. The prevalence of elevated TSH due to macro-TSH was found to be 0.6%.

Conclusion

Discordance between TSH and Free T3 and FreeT4 results, without clinical signs or symptoms of hypothyroidism are considered as having an immunological interference by heterophile antibodies or that we are in the presence of a form of macro-TSH consisting of an immune complex bound to the anti-TSH autoantibody. Analytic-antibody complexes are a well-known cause of clinical misinterpretation of endocrine results.

AUTO1-0024
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

RAMADAN FASTING EXERTS IMMUNOMODULATORY EFFECTS AND GENERALLY DOES NOT AFFECT IMMUNOLOGIC MARKERS IN CLINICAL AND NON CLINICAL POPULATIONS: INSIGHTS FROM A SYSTEMATIC REVIEW

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Background

Ramadan is the ninth month of the Islamic lunar calendar, and is observed by Muslims as a month of fasting. All Muslim adults are expected to fast, nevertheless certain subgroups are exempted including the sick, frail and pregnant women among others. Ramadan fasting have been shown to impact body systems in different manners. The influence of Ramadan fasting on immune system regulation remains elusive, however. Regulating body response to various infectious, stressful and other harmful events, immune system changes are of great interest during fasting.

Method

In this paper, we performed an extensive systematic literature review of ISI Web of Science (WoS), Scopus, MEDLINE/PubMed, Google Scholar, DOAJ, EbscoHOST, Scirus, Science Direct, the Cochrane Library and ProQuest using using the following key words: “fasting”, “Ramadan”, “Islam”, and “immunity”.

Results

see later

Conclusion

Conclusions drawn from these findings included: 1- Ramadan fasting has been shown to only mildly influence the immune system and the alterations are transient and return to basal pre-Ramadan status. 2- Ramadan fasting during the second trimester of pregnancy was shown to be safe and did not result in negative fetal outcomes, or maternal oxidative status alterations.3- In cardiac patients, Ramadan fasting can have beneficial effects including lipid profile improvement and alleviation of oxidative stress. 4-In asthmatic patients as well as in patients with HIV/AIDS and autoimmune disorders, fasting was safe. 5-In psychiatric patients, such as those suffering from schizophrenia, fasting could increase immunologic markers. 6- Fasting Muslim athletes who maintain intensive training schedule during Ramadan show fluctuations of immune markers.

AUTO1-0049
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

MILK, HUMAN NUTRITION AND AUTOIMMUNITY.

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Background

Humans started to drink other mammals milk 11,000 years ago. Both incidence of allergies to cow milk and autoimmune diseases have risen in the western industrialized countries, where milk is a major dietary component especially of processed foods. The "mosaic of autoimmunity" elucidates the diversity and multifactorial origin of autoimmune disease expression in humans. Growing evidence suggests a large overlap between oral tolerance, food antigens and autoimmune diseases. Allergenic milk proteins associated with an immature and susceptible immune system in children is an important threat for future health.

Method

Literature review.

Results

Several studies have shown strong evidence that exposure to cow´s milk during childhood can influence the risk of developing many autoimmune diseases, such as type 1 diabetes, celiac disease, inflammatory bowel disease, rheumatoid arthritis, juvenile idiopathic arthritis, idiopathic membranous nephropathy, multiple sclerosis, Behçet's disease, autoimmune uveitis, schizophrenia and bipolar disease. Assorted mechanisms have been hypothesized to explain the connection between these entities, mainly involving molecular mimicry, shared epitopes, cross-reactivity phenomena, changes in host gut permeability, microbiome and even through chronic infections.

Conclusion

The consumption of cow´s milk should be reconsidered among subjects with high susceptibility to develop autoimmune diseases, since the exposure could represent a trigger for the disease onset.

AUTO1-0714
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

FOOD INTOLERANCE IN PATIENTS WITH AUTOIMMUNITY

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Background

Dr Francis Coucke, Anne-Birgitte Vogter

Leaky gut leads to autoimmunity e.g. in coeliac disease. There is little information about correlation between food intolerance and autoimmunity except for gluten intolerance. This facts form the rationale to examine food intolerance in patients with autoimmune diseases.

Method

A food intolerance was performed in 100 patients seen at our clinic between January 2016 and September 2017 with outimimmune diseases. Mean age is 45 with 89 females. A control group consists of 20 patients without any autoimmuinty. Mean age is 43 and 15 females.

A food intolerance test on the base of igG specific antibodies against 50 food was performed.

Results

We found more elevated antibodies and higher levels of food igG antibodies which are a sign of immune intolerance in patients with autoimmune diseases compared to controls.

The highest score was found for:

Antigens	Patients (u/ml)	Normals (u/ml)
Caseine	58	5
Cow milk	79	20
Goat milk	42	10
Wheat	46	31
Gliadine	28	9
Yeast	48	25

Conclusion

This abstract shows clearly high titers of food antibodies in autoimmune patients. Modifying diet according to intolerance could be useful. Highest foodintolerance values were found for casein and cow milk proteins, which could suggest that these products should be avoided in autoimmune patients. Individual testing in all patients with autoimmune disease should be done in clinic and food advise based on antibodies should be given to the autoimmune patients.

AUTO1-0015
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

THE ANATOMY OF THE DEATH CASES FROM HPV VACCINE SUPPORTED BY VAERAS REPORT

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Background

Dietary habits have long been known to have a crucial influence on human health, affecting the risk for hypertension, heart diseases and stroke, as well as influencing the development of cancer. Therefore, when considering the complex web of factors compiling the mosaic of autoimmunity, it is not surprising that various novel dietary elements were recently found to play a role in disease development and prevention.

Method

Today, we are facing a new era of digitization of the healthcare system. With the wide spread availability and accessibility of quality health data and information, there is a growing demand for safe, cost effective and simple to administer therapies. Moreover, autoimmune rheumatic diseases are chronic diseases, such that accompany patients through their lives and are greatly influenced by the life style of their carrier. In light of this, it stands to reason that the search for additional therapies to attenuate these diseases would lead to investigating life style modifications.

Results

In this article we reviewed an attractive alternative to conventional therapeutics – our diet. We chose to focus on several common nutritional components in the human diet, for which there are relevant, interesting evidence as to their effect on rheumatic autoimmune diseases.

Conclusion

In this article we reviewed an attractive alternative to conventional therapeutics – our diet. We chose to focus on several common nutritional components in the human diet, for which there are relevant, interesting evidence as to their effect on rheumatic autoimmune diseases.

AUTO1-0036
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

CORRELATION OF DIETARY AQUAPORIN IMMUNE REACTIVITY AND NEUROLOGICAL TISSUE ANTIBODIES IN SELECTED PATIENT SPECIMENS

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Background

Specific food aquaporins have been shown to share homology with human aquaporin. Thus, antibodies formed against the dietary aquaporin may cross-react with brain aquaporin, leading to blood-brain barrier permeability, and neuroautoimmunity. This study aimed to examine the correlation between food aquaporin antibodies and nervous system antibody formation.

Method

We selected an equal number of male and female patients who resulted IgG + IgA positive to at least one food aquaporin (cooked corn + corn aquaporin, soybean oleosin + soy aquaporin, raw spinach + spinach aquaporin, raw tomato + tomato aquaporin) and were simultaneously assessed for neurological (IgG + IgA to myelin basic protein, asialoganglioside, alpha + beta tubulin, cerebellar, synapsin) antibodies. We compared the quantity of food aquaporin positives to neurological immune reactivity.

Results

Of the patient population positive for 1, 2, 3 and 4 food aquaporins, 41%, 54%, 60% and 100% respectively, made antibodies against at least one neurological protein.

Conclusion

The percent of neurological tissue antibody production increased with the number of positive food aquaporins. Of the four food aquaporins, spinach was the most common reactive. Of the neurological tissues assessed, tubulin was the most common positive. Patients with antibody reactivity to dietary aquaporins may consider abstaining from the aquaporin-containing food in order to prevent neurological tissue damage.

AUTO1-0621
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

FOOD ADDITIVES, DYSBIOSIS AND INTESTINAL PERMEABILITY: POTENTIAL INDUCERS OF AUTOIMMUNITY

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Background

The incidence of autoimmune diseases (AD) is increasing along with the expansion of industrial food processing and food additive consumption.
The intestinal epithelial barrier, with its intercellular tight junction, controls the equilibrium between tolerance and immunity to non-self-antigens. As a result, particular attention is being placed on the role of tight junction dysfunction in the pathogenesis of AD. Tight junction leakage is enhanced by many luminal components, commonly used industrial food additives being some of them.

Method

Glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase, and nanoparticles are extensively and increasingly used by the food industry, claim the manufacturers, to improve the qualities of food. However, all of the aforementioned additives increase intestinal permeability by breaching the integrity of tight junction para-cellular transfer.

Results

In fact, tight junction dysfunction and dysbiosis are common in multiple ADs and the central part played by the dysbiota and the leaky gut in ADs pathogenesis is extensively described. It is hypothesized that commonly used industrial food additives, impact the microbiome and abrogate human epithelial barrier function, thus, increasing intestinal permeability through the opened tight junction, resulting in entry of foreign immunogenic antigens and activation of the autoimmune cascade.

Conclusion

Future research on food additives exposure-dysbiosis-intestinal permeability–autoimmunity interplay will enhance our knowledge of the common mechanisms associated with autoimmune induction, maintenance and progression.

AUTO1-1073
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

ELECTROSMOG RADIATION - LIKELY EFFECTS ON THE VDR

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Between 68% and 75% of European physicians have been consulted about Electromagnetic Hyper-Sensitivity (EM, EHS). Although many feel that the patient reports sound plausible, scientists have failed to provide them the guidance needed to fully understand what might be happening. Some have nevertheless come up with answers - Karolinska's Olle Johansson demonstrated that these invisible waves interfere with the human immune system, while Martin Pall found that they alter calcium metabolism. Dominique Belpomme has suggested some biomarkers he has found useful in diagnosis, and some physicians, such as California's Scott Eberle, have themselves succumbed, publicly blogging their own experiences.

The WHO has been no help, with its pronouncements dominated by industry. However, Gro Harlem Bruntland, retired General Director of the WHO, has publicly been warning about the risks of EM radiation to public health, stating that she has no doubt that humans are negatively affected by Electrosmog, "We have to hope that it doesn't turn out too seriously."

Somewhere between 2 and 10% of the population report that they are sensitive to cellphones and WiFi.. Yet we reported last year that EHS seemed much higher in 64 volunteers from our autoimmune and chronic disease cohort than either of these numbers, with 90% reporting a definite response to the EM-shielded clothing we designed for that study. Further, we used advanced Molecular Dynamics to show that the Vitamin-D Receptor molecule, the VDR, was itself susceptible to these invisible fields, finally expounding a solid scientific mechanism for these biological interactions.

So what does an Autoimmunologist need to know? The last 3-4 years have seen an explosion in Electrosmog, due to the build-out of new 4G towers and the rapid penetration of WiFi into the home and workplace. Pediatricians are warning of potential dangers to kids, and of dangers to the unborn. But it would seem that the risk to those whose immune systems are already struggling, those with chronic and autoimmune conditions, is far greater.

Some patients have come to rely on the immunosuppression created by their gadgets, and become very ill when sleeping in a Faraday Cage (which totally blocks out the radiation, allowing the immune system to recover). As they live their lives, travelling between high and low radiation extremes, their symptoms wax and wane regardless of any therapy they are receiving.

We will discuss some of the options available to help mitigate these symptom surges, and explore how Autoimmunology might well be fundamentally changed by the advent of Electrosmog.

AUTO1-0176
ENVIRONMENT, NUTRITION AND AUTOIMMUNITY

COFFEE AND AUTOIMMUNITY: MORE THAN A HOT BEVERAGE

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Background

Coffee consumption has gained a great deal of interest due to its health impact as well as a result of being one of the world's most consumed beverage. Recent evidence showed that coffee intake was associated with decreased mortality in cardiovascular, neurological, diabetes type II, as well as endometrial and liver cancer. Possible links between coffee intake and the development and progression of autoimmune disease have been suggested.

In this review, basing on the available data in the literature, we aimed to investigate the association between coffee and its influence on the immune system and the relevant autoimmune diseases. Caffeine, as a major constituent of coffee, was found to have an immunomodulatory action on the immune system. While some studies were found to be conflicting, general trends have been identified. Coffee consumption increased the risk for Rheumatoid arthritis, Type 1 Diabetes mellitus. In constrast, coffee consumption showed a protective role against multiple sclerosis, primary sclerosing cholangitis, and ulcerative colitis disease development. In other autoimmune diseases such as systemic lupus erythematosus, psoriasis, primary biliary cirrhosis and crohn's disease no significant association was documented with coffee consumption. While in other instances, coffee consumption was shown to influence disease course and management options. Coffee intake was led to a decrease in insulin sensitivity in Type 1 Diabetes Mellitus, a lowering of methotrexate efficacy in rheumatoid arthritis, a decreased levothyroxine absorption in Hashimto's disease, and finally la cross reactivity with gliadin antibodies in celiac patients.

Method

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Results

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Conclusion

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AUTO1-0326
ERIC GERSHWIN'S SESSION ON AUTOIMMUNITY

SPONTANEOUS AUTOIMMUNE SCLERODERMA/SYSTEMIC SCLEROSIS IN UCD-200 CHICKENS – OPPORTUNITIES AND LIMITATIONS

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Background

To study multifactorial, non-communicable diseases such as autoimmune disorders, animal models that spontaneously but predictably develop the condition and exhibit clinical and biological manifestations of the disease in humans are critical.

Method

For systemic sclerosis/scleroderma (SSc), an autoimmune connective tissue disorder with fibrosis of internal organs and skin, one such animal model is the UCD-200 chicken.This avian SSc model was developed and introduced to the medical research community by Dr. Eric Gershwin and collaborators at the University of California-Davis (UCD) in 1981.

Results

With Dr. Gershwin's leadership, primary phenotypic characteristics and autoimmune components involved in this disease were established and the UCD-200 chicken was accepted as a rare biomedical research model for spontaneously developing SSc. Development of international collaborations and adoption of the UCD-200 line by researchers at Medical Schools in Europe (Innsbruck, Austria, and Uppsala, Sweden) led to valuable new insights on genetic-susceptibility, immunopathological mechanisms, target cell physiology, presence of environmental triggers, and aberrant fibrotic activity in SSc. Unfortunately, development of research tools and the limited ability of research institutions to maintain chicken populations, constituted challenges to research progress.

Conclusion

Recent adoption of the UCD-200 line by the University of Arkansas, together with availability of current research tools for the avian system (e.g. global genome resequencing, transcriptomic and proteomic gene-expression studies; epigenetic, metabolomic and microbiome analyses; availability of chicken-molecule specific reagents; etc.) afford continued incorporation of this valuable animal model in basic biomedical and translational research on SSc, as well as, in the development of treatment and prevention strategies.

AUTO1-0260
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

MODULATION OF IMMUNE ACTIVATION AND REDUCTION OF AUTOANTIBODY PRODUCTION BY SOLUBLE MHC-II MOLECULES IN A SLE MURINE EXPERIMENTAL IN VITRO AND IN VIVO MODEL

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Background

Systemic lupus erythematosus (SLE) is a multiparametric and severe condition with variable symptoms and at the present time no effective therapeutic approaches have been applied. In our study we took advantage of the recently described role of soluble major histocompatibility complex class II (sMHCII) molecules (present in most body fluids of healthy individuals and various pathological conditions) in maintaining tolerance to the organism and attempted to apply sMHCII proteins as a treatment to murine SLE experimental models *in vitro* as well as *in vivo*.

Method

Syngeneic or allogeneic sMHCII molecules, purified from healthy mouse serum and verified by ELISA, SDS-PAGE and Lowry method were used.

Results

After breaking tolerance to DNA *in vitro*, which was accompanied by development of specific anti-dsDNA antibodies, sMHCII could significantly reduce the specific antibody levels and drive the system towards immunosuppression, as assessed by specific marker analysis on T cells and cytokine production by flow cytometry and ELISA respectively. The in vivo experimental model consisted of pristane-induced SLE symptoms to BALB/c mice, which developed maximal levels of anti-dsDNA two months after pristane inoculation. Syngeneic or allogeneic sMHCII administration could alleviate pristane-induced symptoms, significantly decrease specific anti-dsDNA antibody production and develop immunosuppression to the host, as manifested by increase of CD4+CTLA-4+ and CD4+CD25+ cell populations in the spleen.

Conclusion

Thus, the results presented in this study, introduced the ability of sMHCII proteins to suppress specific autoantigen response, opening new areas of research and offering novel therapeutic approaches to SLE with expanding features to other autoimmune diseases as well.

AUTO1-0337
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

IMMUNE RESPONSES TO PEPTIDES CONTAINING HOMOCITRULLINE OR CITRULLINE IN THE DR4-TRANSGENIC MOUSE MODEL OF RHEUMATOID ARTHRITIS

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Background

Antibodies to proteins/peptides containing citrulline are hallmarks of Rheumatoid Arthritis (RA). These antibodies are strongly associated with the expression of the Shared Epitope (SE). RA patients also generate antibodies to homocitrulline-containing proteins/peptides (also referred to as anti-carbamylated protein antibodies (Anti-CarP)). This study was undertaken to investigate the relationship between homocitrulline and citrulline immune responses using an established mouse model of RA: DR4-transgenic (DR4tg) mice that express the human SE.

Method

C57BL/6 (B6) and DR4tg (on a B6 background) mice were immunized subcutaneously with a homocitrullinated peptide (HomoCitJED). Splenic T cell proliferation was evaluated by 3H-thymidine incorporation assay. Antibodies to homocitrullinated and citrullinated antigens were screened by enzyme-linked immunosorbent assay (ELISA). Antibody cross-reactivity was examined by inhibition with HomoCitJED and its citrullinated counterpart peptide, CitJED (the number of homocitrullines in HomoCitJED is equal to the number of citrullines in CitJED).

Results

HomoCitJED-immunized DR4tg mice developed early T and B cell responses to HomoCitJED and late responses to CitJED. These mice also developed anti-CCP2 antibodies. In some mice, antibodies to HomoCitJED were also reactive to CitJED. B6 mice immunized with HomoCitJED developed late T and B cell responses to HomoCitJED, but did not generate responses to citrullinated antigens. Unlike DR4tg mice, anti-HomoCitJED antibodies from B6 mice did not react to CitJED.

Conclusion

DR4tg mice immunized with HomoCitJED developed immune responses to CitJED, indicating cross-reactivity. CitJED immune responses were dependent on the SE. HomoCitJED responses occurred in the absence of the SE (B6 mice); however, they developed earlier in DR4tg SE-expressing mice.

AUTO1-0449
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

ZAP-70 CONTROLS AUTOIMMUNE ARTHRITIS VIA ALTERATIONS IN T CELL ACTIVATION AND APOPTOSIS SENSITIVITY IN MICE

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Background

The recombinant human G1(rhG1)-induced arthritis (GIA) model resembles human rheumatoid arthritis in many aspects. ZAP-70 kinase is a key molecule of T cell receptor signaling; T cell activation and apoptosis has been shown to critically regulate arthritis severity.

Previously we have shown that partial ZAP-70 deficiency ameliorates autoimmune arthritis in the GIA model, using both *in vivo* (decreased severity and milder arthritis) and *in vitro* experiments (decreased T cell proliferation, IL-4 and IL-6 production).

Method

To test the hypothesis that the above changes are due to complex alterations in T cell signaling, we performed T cell activation experiments. T cells were isolated from healthy and arthritic BALB/c and ZAP-70 heterozygous (ZAP-$70^{+/-}$) knockout animals, then stimulated for 24 or 48 hours with anti-CD3/anti-CD28-coated beads. In some experiments, T cells isolated from arthritic mice were pre-treated with rhG1.

Results

We have seen decreased tyrosine phosphorylation, cleaved caspase-3 and phosphorylated NFκB expression in healthy ZAP-$70^{+/-}$ animals after stimulation. In these samples Erk phosphorylation was only detectable after 48 hours. In arthritic mice tyrosine phorphorylation patterns were similar in ZAP-$70^{+/-}$ and BALB/c animals. Interestingly in arthritic mice pre-treatment of isolated T cells with rhG1 inhibited tyrosine phosphorylation even after stimulation with beads.

Conclusion

Our results show that the partial deficiency of ZAP-70 results in altered T cell activation through the T cell receptor complex, accompanied by decreased apoptosis sensitivity of T cells which might translate into less severe arthritis.

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AUTO1-0402
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

INTERFERON-ALPHA PROTECTS AGAINST PAIN AND JOINT DAMAGES IN EXPERIMENTAL INFLAMMATORY ARTHRITIS THROUGH EXPANSION OF HIGHLY SUPPRESSIVE REGULATORY T LYMPHOCYTES

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Background

Type I interferons (IFN-I) can be both anti- and pro-inflammatory. Their role is controversial in rheumatoid arthritis (RA) and experimental models. We have evaluated for the first time the therapeutic effect of IFN-α in collagen-induced arthritis (CIA) which mimics RA.

Method

Disease was induced by 2 immunizations with collagen/CFA in conditional transgenic mice over-expressing IFN-α1 and non-transgenic littermates. Arthritis was followed by clinical evaluation/histology. Pain was followed by stance/Von Frey tests. Plasma cytokines/anti-collagen antibodies were measured by Luminex/ELISA. Leukocytes sub-populations/polarization were analyzed by flow cytometry. Osteoclasts were prepared from the bone marrow (BM). $CD4^+CD25^+$ regulatory T cells (Treg) and $CD4^+CD25^-$ effector T cells (Teff) were purified by magnetic sorting. ATPase activity was determined in vitro. Treg inhibition of Teff activation was measured by flow cytometry/ELISA. The in vivo therapeutic capacity of purified Treg was estimated by adoptive transfer.

Results

IFN-α1 induction before the first or even between both immunizations resulted in CIA protection/lower pain. Anti-collagen antibody/IL-6 production were lower in IFN-$\alpha1^+$ mice. Protected mice show decreased polarization to Th17 and increased polarization to Th2 and IFN-γ-positive Th1/NK cells. CIA protection in IFN-α1-overexpressing mice was associated with lower osteoclastogenesis/osteoclast activity, impaired BM-B cells, increased BM-$CD86^+$ neutrophils, and particularly expansion of Treg with higher CD39/CTLA-4 expression, higher ATPase activity and higher suppressive capacity. Adoptive transfer of Treg purified from CIA-IFN-$\alpha1^+$ mice impaired CIA development in recipients in comparison to Treg purified from CIA-IFN-$\alpha1^-$ mice.

Conclusion

IFN-α1 protects against inflammatory arthritis, even in mice already seropositive, clarifying its role and showing its potent modulatory effect.

AUTO1-0286
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

PHOTOBIOMODULATION THERAPY PREVENTS EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS MODEL

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Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the central nervous system (CNS) of unknown etiology and heterogeneous clinical symptoms/course. MS symptoms include numbness, muscle spasms, optic neuritis and neuropathic pain. The existing therapies for MS are only partially effective and are associated with undesirable side effects. Photobiomodulation (PBM) or low-level laser therapy (LLLT) has been clinically used to treat inflammation, and to induce tissue healing and repair processes.

Method

However, there are no reports about the effects and mechanisms of PBM in experimental autoimmune encephalomyelitis (EAE), an established model of MS.

Results

Our study demonstrated that PBM (AlGaInP, 660 nm and GaAs, 904 nm), irradiated on the spinal cord during EAE development, showed neuroprotective effects against EAE diminishing both clinical signs and weight loss typical of disease. Moreover, histological analysis showed that PBM blocked neuroinflammation through reduction of inflammatory cells into the CNS, especially lymphocytes, as well as prevented demyelination in the spinal cord after EAE induction. Furthermore, these beneficial effects of PBM seem to be associated with down-regulation of NO levels in the CNS, although treatment with PBM failed to inhibit lipid peroxidation and restore antioxidant defense during EAE. In particular, elevated IL-17, IFN-γ and IL-1β levels in the spinal cord tissues, a result of EAE, was reversed with PBM treatment in EAE mice.

Conclusion

On these bases, we propose that PBM may be a promising non-pharmacological disease-modifying therapy for the treatment of autoimmune conditions, such as MS.

AUTO1-0535
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

ABSENCE OF NKX2.3 TRANSCRIPTION FACTOR AMELIORATES AUTOIMMUNE ARTHRITIS IN MICE

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Background

The recombinant human G1(rhG1)-induced arthritis model is an experimental autoimmune arthritis model resembling human rheumatoid arthritis in many aspects. Arthritis can be induced by immunizing mice with BALB/c background with the rhG1 domain of human proteoglycan aggrecan. Mice deficient for Nkx2.3 homeodomain transcription factor show a defective splenic red pulp structure coupled with altered homing of lymphocytes to the intestine and increased levels of TH17 cells.

Method

To test the effect of this splenic stromal deficiency on the development of autoimmune arthritis, wild-type BALB/c (WT) and Nkx2.3 homozygous knockout ($Nkx2.3^{-/-}$) mice were immunized with rhG1 side-by-side once every three weeks for three times. Clinical symptoms were scored, T cell mediated immune responses were investigated by measuring cytokine production and anti-rhG1 antibody production from *in vitro* splenocyte cultures and sera.

Results

We have found that both severity and incidence of arthritis in $Nkx2.3^{-/-}$ mice were significantly reduced in comparison to WT. *In vitro* tests showed no inflammatory cytokine production in $Nkx2.3^{-/-}$ samples after stimulation with rhG1, while in WT significant IL-6, IL-17, TNF-α, IFN-γ and IL-4 production was measured. In the sera antigen-specific IgG1 levels were signifcantly decreased in $Nkx2.3^{-/-}$ mice.

Conclusion

Our results suggest that autoimmune arthritis develops even in the absence of a normal spleen structure in Nkx2.3-deficient mice. However, the milder clinical picture associated with decreased autoantibody production shows that altered lymphocyte recirculation influences the pathogenesis of GIA.

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AUTO1-0488
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

MUTUAL EFFECT OF PROGESTERONE IN MOUSE MODEL OF SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis is an autoimmune disease of connective tissue with increased incidence in females. Several factors explain the predominance of autoimmune disorders in female and among them sex hormones could play a major role. Progesterone, the female sex hormone may influences autoimmunity through direct effect on functionality of parenchymal cell or by its immunomodulatory effect. Information concerning the effect of progesterone on systemic sclerosis are very few therefore in this study we examined the effect of progesterone on bleomycin– induced fibrosis in female BALB/c mice.

Method

Mice with bleomycin- induced fibrosis received progesterone for 21 and 28 days. After 28 days, blood were collected for hormone and cytokine measurement, and under lethal anaesthesia bronchoalveolar lavage were collected for cell counting, skin and lung tissues were harvested for histological assessment and hydroxyproline measurement

Results

Pathological evaluation and hydroxyl proline measurement indicated that the content of collagen in lungs but not in skin tissues in progesterone treated mice were increased. Progesterone caused the decline of serum level of TNF-α and increased serum level of cortisol in bleomycin injured mice ($P < 0.05$).

Conclusion

Our data showed that progesterone has mutual effect on skin and lung tissue of bleomycin treated female mice.

AUTO1-0586
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

DIFFERENTIAL GENE EXPRESSION PROFILE AND IMMUNE RESPONSE TO HSP65 MODULATE SUSCEPTIBILITY TO AUTOIMMUNE ARTHRITIS IN RATS

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Background

The major histocompatibility complex (MHC) has a profound influence on immune response to potential autoantigens, and thereby on the induction of autoimmunity. We previously reported differential susceptibility to adjuvant-induced arthritis of MHC-compatible (RT.1^{l}) Lewis (susceptible) and WKY (resistant) rats. To gain insight into this disparate disease phenotype, we examined the gene expression profiles of these rats following an arthritogenic challenge.

Method

Rats were immunized with heat-killed *M. tuberculosis* H37Ra. After 7 d, the total RNA of their draining lymph node cells (LNC) was tested using oligonucleotide-based DNA microarray chip. The data was statistically analyzed to determine and compare the differentially expressed genes (DEG). In addition, the association of the DEG with arthritis-related quantitative trait loci (QTL) was analyzed.

Results

The overall immune responsiveness of WKY rats was higher than that of Lewis rats. In addition, significant differences were observed in the association of DEG with rat arthritis-QTL in the two strains. The number of genes showing enhanced expression as well as association with QTL were higher in Lewis rats compared with WKY rats. On the contrary, genes showing reduced expression as well as association with QTL were higher in WKY rats than Lewis rats. Differences were also observed in the Th17/Treg ratio and cytokine responses of the two strains.

Conclusion

Arthritis-susceptible versus resistant phenotype of MHC-compatible rats correlates with distinct patterns of gene expression and immune response to the disease-related antigen. These results would contribute to our understanding of the pathogenesis of autoimmune arthritis, and might also offer potential novel therapeutic targets.

AUTO1-0452
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

FUNCTIONAL ROLE OF DEXAMETHASONE PRE-TREATED REGULATORY T CELL TRANSFER IN THE DEVELOPMENT OF MURINE AUTOIMMUNE ARTHRITIS

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Background

Previously, we showed the resistance of regulatory T cells (Tregs) to glucocorticoid-induced apoptosis and their increased suppressor cytokine production after high-dose *in vivo* dexamethasone (DX) treatment of mice. Since T cells are important mediators of autoimmune diseases, to test the function of these Tregs we used the recombinant human aggrecan G1-domain (rhG1)-induced arthritis model (GIA), which resembles the human rheumatoid arthritis in many aspects.

Method

BALB/c mice were injected daily with high-dose DX four times before the arthritis induction by immunization with rhG1 antigen once every three weeks for three times. The clinical symptoms were assessed using a scoring system. After the last immunisation, mice were sacrificed; and their splenocytes were *in vitro* stimulated to investigate antigen-specific T cell proliferation and cytokine production (IL-1β, IL-4, IL-6, IL-10, IL-17, IFNγ, TNFα, TGFβ). Splenic Tregs, isolated from the DX pre-treated mice, which developed the least or most severe arthritis, were transferred into untreated BALB/c mice before their immunisation with rhG1.

Results

The DX pre-treated mice developed less severe arthritis compared to controls. T cell proliferation and cytokine production were altered. Mice, receiving Tregs from DX pre-treated donors with less severe arthritis, developed less pronounced arthritis than the control group.

Conclusion

In conclusion, the high dose DX pre-treatment reduced the severity of arthritis in GIA model, and GC pre-treated, probably antigen-specific, Tregs might play a role in decreasing the severity of arthritis.

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AUTO1-0368
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

A PROTEOMIC ANALYSIS OF FIBROBLAST-LIKE SYNOVIOCYTE TREATED WITH TNF-A

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Background

Rheumatoid arthritis (RA) is a polyarticular inflammation, in which hyperplasia of the synovial cells is observed along with inflammatory mononuclear cell infiltration and angiogenesis. A characteristic synovial expansion by angiogenesis and subsequent destroying of the cartilage are also observed in RA. The molecular network in RA is quite complicated, with a lot of cytokines or mediators conferring various actions and many different target protein.

Method

To investigate the pathogenesis of RA, we applied proteomic analysis to determined the protein profile in fibroblast-like synoviocyte, MH7A. This synovial cell line was established from patients with RA. Proteins were extracted from MH7A that were stimulated with tumor necrosis factor-a (TNF-α). We used nano LC-MS/MS proteome-analysis system with a long monolithic silica capillary column for investigation into the molecular mechanism of RA.

Results

After proteomic analysis on proteins from untreated MH7A and those from MH7A stimulated with TNF-α, we selected 269 differentially produced proteins that were detected only under TNF-α stimulation. These proteins and classified these proteins by performing gene ontology analysis are going to be introduced in a presentation.

Conclusion

We detected substantial production of plasminogen activator inhibitor 2 and several apoptosis-regulating molecules in TNF-α-stimulated MH7A cells. Experimental results suggest that these upregulated proteins might contribute to the pathogenesis of RA.

AUTO1-0004
EXPERIMENTAL MODELS & AUTOIMMUNE DISEASES

CONTROL OF ANTI-SELF-REACTIVITY BY MULTI-POTENT MESENCHYMAL STROMAL CELLS OR RE-INDUCTION OF SELF-TOLERANCE BY AUTOLOGOUS STEM CELLS FOLLOWING LYMPHOABLATIVE CONDITIONING

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Background

Multi-potent mesenchymal stromal cells (MSC) induce regulation of inflammation potentially effective for treatment of autoimmune diseases (AID). Bone marrow, fat tissue and placenta & cord tissue derived MSCs can be expanded in culture and used for a broad spectrum of indications. MSCs migrate spontaneously to sites of inflammation and damage and as such used for treatment of organ-specific AID. We pioneered using bone marrow derived autologous MSCs for multiple sclerosis (MS) and other neurodegenerative disorders aiming to turn off inflammatory phase of MS, possibly also re-myelination since we documented that MSCs can differentiate into neurons and glial cells, oligodendrocytes included.**Method**

Based on successful pilot study in 13 patients with MS and 14 with amyotrophic lateral sclerosis (ALS), a total of >400 patients were treated using 10^6 autologous MSC/Kg intrathecally + 0.5 – 1.5x10^6 MSC/Kg intravenously.

Results

Best results were observed in 70% MS patients with objective improvement of EDSS scores.

Conclusion

Safe MSCs treatment for AID should be evaluated against attempting re-induction self-tolerance by more hazardous lymphoablative, yet safer than myeloablative conditioning, aiming to eliminate all self-reactive lymphocytes followed by infusion of autologous hematopoietic stem cells for establishing new immune system, anticipating apoptosis of all self-reactive lymphocytes interacting against antigens that may activate the autoimmune process in *status nascendi*, reproducing the normal ontogeny of the immune system in utero. Taken together, both procedures can benefit patients with life-threatening AID. The procedure of choice should be based on fully personalized basis, depending on disease severity, response to conventional treatment and patient's general condition.

AUTO1-0178
GENETICS AND AUTOIMMUNITY

NEW DEVELOPMENTS IN THE "X CHROMOSOME-NUCLEOLUS NEXUS" HYPOTHESIS OF AUTOIMMUNE DISEASES

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Background

The “X chromosome-nucleolus nexus” hypothesis presented the concept that stress causes the nucleolus to expand and, due to its close proximity to the inactive X chromosome (a.k.a. Barr body), the expanding nucleolus could disrupt the Barr body opening previously sequestered X-linked genes. Genes from Xp22 and the pseudo-autosomal region 1 (PAR1) are suspected of roles in generation of abnormal endogenous material that can trigger an autoimmune reaction. Among these genes are: a “hot” LINE1 reverse transcriptase; a fragile site, FRAXB, that could contain latent viruses; two polyamine genes, spermine synthase (SMS) and spermidine/spermine N1 acetyltransferase (SAT1) involved in polyamine synthesis and recycling, respectively; and a large cluster of Alu elements in PAR1. LINE1 reverse transcription could lead to autoantigenic hypomethylated DNA. A large amount of Alu RNA from PAR1 could serve as substrates for the LINE1 reverse transcriptase. Altered polyamine synthesis and recycling could reduce S-adenosylmethionine (SAM) needed for cellular methylation. And latent viruses in FRAXB could become active causing further stress.

Method

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Results

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Conclusion

The hypothesis can now be expanded to explain how nucleoli can be disrupted from activity of the disrupted Barr body. Alterations of polyamine levels and/or an abundance of RNA polymerase III transcribed Alu RNA can disrupt the nucleolus causing slower response to cellular stress and nucleolar fragmentation. Nucleolar dysfunction can lead to incomplete or misassembled ribonucleoproteins (RNPs), such as ribosomal and spliceosomal subunits, that now present altered epitopes that provoke an immune reaction. Many autoantigens in lupus are, at least transiently, components of the nucleolus.

AUTO1-0065
GENETICS AND AUTOIMMUNITY

BEYOND APECED: THE ROLE OF THE AUTOIMMUNE REGULATOR GENE IN PHYSIOLOGY AND DISEASES

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Background

Immune tolerance is a crucial feature of the immune system that ultimately allows the elimination of foreign antigens, avoiding collateral damage to host tissues. Immune tolerance can be classified into: 1) central tolerance, occurring during lymphocyte development in the primary lymphoid organs; 2) peripheral tolerance, that takes place in the peripheral tissues and lymph nodes. At the thymic level, the induction of tolerance to self-antigens is regulated by the autoimmune regulator gene (AIRE) expressed by the medullary thymic epithelial cells (mTECs). AIRE promotes the expression by mTECs of different tissues-specific antigens (TSAs) typically expressed at the periphery. Self-reactive T cells having high affinity for the cognate autoantigen are deleted (*via* the process of negative selection) or, alternatively, switched to regulatory T (Treg) cells. Similarly, in peripheral lymphoid organs, extrathymic AIRE-expressing cells (eTACs) eliminate the mature autoreactive T cells or mediate their transformation into non-functional T cells. As consequence, mTECs depletion or AIRE deficiency, decrease the expression of self-antigens, including tumor-associated antigens, and leads to the production of auto-reactive T-cells and impaired generation of Tregs. These phenomena potentially predispose to autoimmunity but, at the same time, may enhance antitumor response. The crucial role played by AIRE in central immune tolerance emerged in the studies on the pathogenesis of Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy, a rare inherited polyendocrine/autoimmune disease. Thereafter, several studies found evidences indicating that AIRE impairment might be pathogenically involved in autoimmune diseases and in tumorigenesis.

Method

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Results

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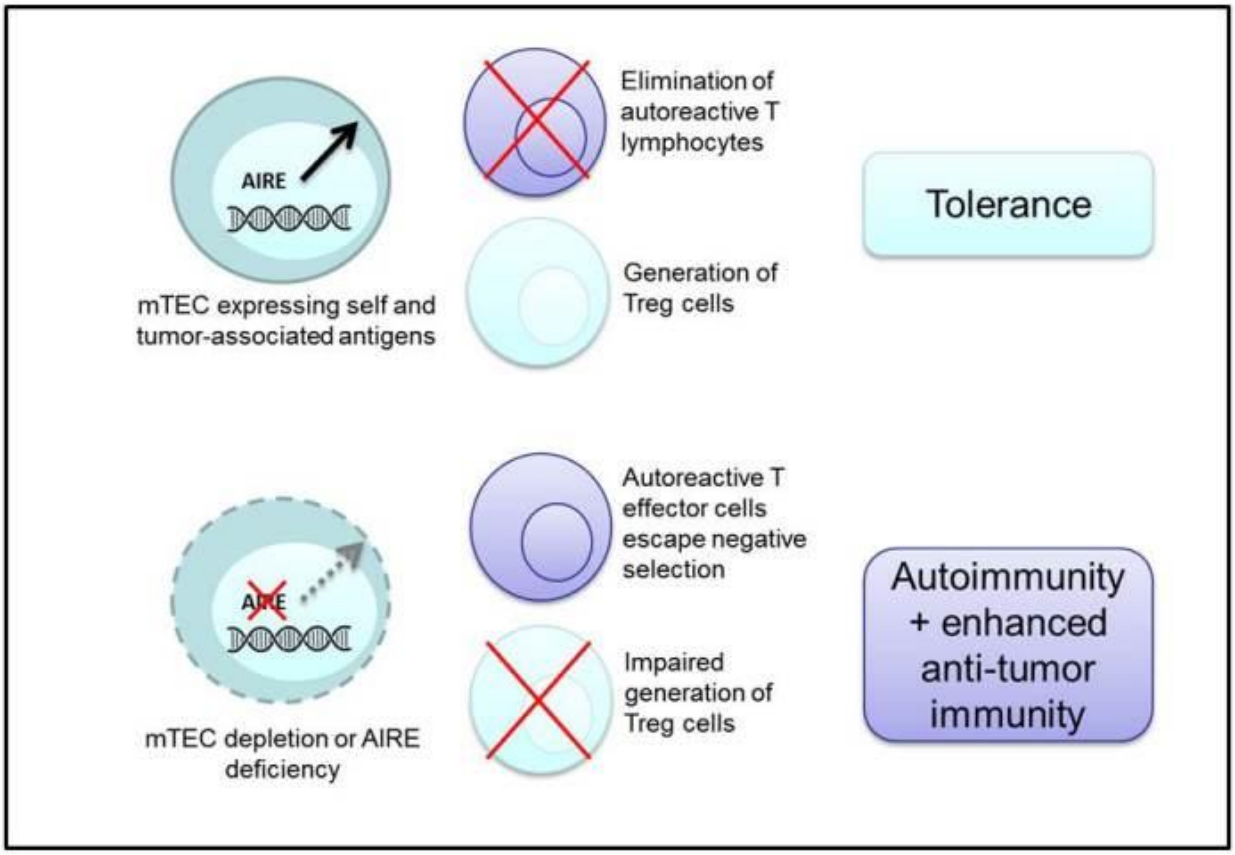
Conclusion


AIRE
mTEC expressing self and tumor-associated antigens
Elimination of autoreactive T lymphocytes
Generation of Treg cells
Tolerance
AIRE
mTEC depletion or AIRE deficiency
Autoreactive T effector cells escape negative selection
Impaired generation of Treg cells
Autoimmunity + enhanced anti-tumor immunity

AUTO1-0339
GENETICS AND AUTOIMMUNITY

DISEASE-SPECIFIC ALTERATIONS IN microRNA EXPRESSION PROFILES IN PRIMARY SJOGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

MicroRNAs (miRNAs) regulate gene expression and modulate various biological processes including immune cell lineage commitment, differentiation, proliferation and apoptosis. A given miRNA may have hundreds of different mRNA targets and a target might be regulated by multiple miRNAs, thus characterisation of dysregulated miRNA expression profiles could give a better insight into the development of autoimmune conditions.

Method

We enrolled eight primary Sjögren's syndrome (pSS) patients, 8 systemic lupus erythematosus (SLE) patients and 7 healthy controls in the study. MiRNAs were isolated from peripheral blood mononuclear cells, and expression patterns were determined with Illumina next-generation sequencing technology. Since pronounced B-cell hyperactivity and autoantibody production are characteristic features in pSS and SLE, we paid special attention on the association between miRNA expression and altered peripheral B-cell distribution.

Results

In SLE patients 135, while in pSS, 26 miRNAs showed altered expression. Interestingly, 25 miRNAs including miR-146a, miR-16 and miR-21, which were over-expressed in pSS patients, were also over-expressed in SLE. On the contrary, we observed down-regulation of miR-150-5p, which was a novel finding in pSS. Several miRNAs were over-expressed in SLE only, such as miR-148a-3p, miR-152, miR-155, miR-223, miR-224, miR-326 and miR-342. Expression levels of miR-223-5p, miR-150-5p, miR-155-5p and miR-342-3p, which are potentially linked to B-cell functions, showed associations with the altered B-cell proportions.

Conclusion

The observed differences in miRNA expressions and the better understanding of their regulatory mechanisms may help to elucidate the pathogenesis of SLE and pSS. This work was supported by the ÚNKP-17-4-III New National Excellence Program of the Ministry of Human Capacities.

AUTO1-0832
GENETICS AND AUTOIMMUNITY

ASSOCIATION BETWEEN CLASS II HLA AND JUVENILE IDIOPATHIC ARTHRITIS: A META-ANALYSIS

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Background: Juvenile Idiopathic Arthritis (JIA) is a complex disease with a prominent and variable joint involvement, occurring before the age of 16 years. JIA is grouped in several subtypes, according to the number of affected joints, the presence of enthesis involvement, psoriasis manifestations or systemic symptoms. JIA is a multifactorial disease, meaning that undefined environmental factors superimpose to a genetic background to cause the disease. HLA has been established as a fundamental genetic factor and different subtypes of JIA seem to be promoted by different HLA genes. Unfortunately, available studies on HLA genetics of JIA are limited and include small case series.
Objective: Evaluating the role of class II HLA genes in the genetic predisposition of JIA through a meta-analysis.
Materials and Methods: Through a literature research in the main clinical databases (MEDLINE/PubMed, EMBASE, Web of Science e Cochrane), studies evaluating class II HLA in JIA patients were obtained. The study protocol is available on the PROSPERO website. https://www.crd.york.ac.uk /PROSPERO/-
Results: 9 case-control studies satisfied eligibility and inclusion criteria and, then, were used to carry this meta-analysis out. All these studies provided several clinical and genetic aspects, including HLA genes that have been studied and JIA classification. Therefore, the OR associated to the development of different JIA subgroups, according to the presence of specific class II HLA alleles, was obtained.
Conclusions: Our meta-analysis showed that: i) HLA-DRB1*08 is a strong factor predisposing to JIA, both for oligo-articular and poly-articular forms (oJIA>pJIA); ii) HLA-DRB1*01 and HLA-DRB1*04 may be involved in the genetic predisposition of RF+ forms of JIA; iii) HLA-DRB1*11 was confirmed to be predisposing to oligo-articular JIA; iv) HLA-DRB1*04 was confirmed to have a role in systemic JIA.

AUTO1-0974
GENETICS AND AUTOIMMUNITY

IMPORTANT DNA METHYLATION/HYDROXYMETHYLATION MODIFICATIONS IN SALIVARY GLANDS FROM PATIENTS WITH SJÖGREN'S SYNDROME

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Background

Sjögren's syndrome (SS) is a chronic autoimmune epithelitis, and several lines of experiments indicate that multifactorial factors contribute to salivary gland epithelial cells (SGEC) dysfunctions including a combination of environmental factors, lymphocytic infiltrations, genetic predispositions as well as epigenetic defects. Such statement is reinforced by the observation that DNA methylation/hydroxymethylation processes are altered in minor salivary glands from pSS patients.

Method

Analysis of the CpG genome-wide methylome array (HM450K, illumina) in long term cultured SGEC.

Results

Such analysis uncovered 4662 CpG positions corresponding to 2560 differentially methylated CpG (DMC), and 575 genes with two or more DMC sites (DMCs), in SGEC as compared with controls. Further analysis highlighted the interferon pathway, the calcium pathway controlling salivation (hypomethylated) and the Wnt pathway (hypermethylated). A sub-analysis was further done revealing the phosphatidylinositol pathway associated with hydroxychloroquine intake and the shift from interferon type I to type II with mucosa-associated lymphoid tissue (MALT) lymphoma evolution. The simultaneous genomic–epigenomic analysis also revealed significant associations between pSS-associated genetic risk factors and DMCs in SGEC, suggesting that pSS risk factors have the potential to affect DNA methylation-sensitive pathways in lymphocytes and in SGEC.

Conclusion

Altogether, our data, therefore, suggest that alteration of DNA methylation in SGEC may contribute to pSS pathophysiology and evolution to MALT.

AUTO1-0161
GENETICS AND AUTOIMMUNITY

GENETIC VARIATION AND SYSTEMIC LUPUS ERYTHEMATOSUS: A FIELD SYNOPSIS AND SYSTEMATIC META-ANALYSIS

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Background

Systemic lupus erythematosus (SLE) is a multi-systemic severe autoimmune disease which results from the irreversible loss of self-tolerance and impaired molecular responses, especially an altered interferon signature. There has been no study investigating whether the numerous reported loci are “truly” associated with SLE or not.

Method

In this review, we have synthesized all available susceptible loci for SLE retrieved from meta-analyses regarding the association between the individual polymorphisms and SLE. Both observational studies and GWAS were included. Furthermore, Bayesian approaches have been employed, including both false positive report probability (FPRP) and Bayesian false discovery probability (BFDP), to estimate the noteworthiness of the evidence

Results

Among 133 significant genotype comparisons, 45 (34%) were found noteworthy under both false positive report probability (FPRP) and Bayesian false discovery probability (BFDP). From the meta-analysis of genome-wide association studies (GWAS), we could confirm that all significant comparisons were noteworthy under both Bayesian approaches. Both approaches may be advantageous for determining whether the reported associations is genuine, especially for interpreting results from observational studies instead of GWAS whose significance was determined in a more strict manner. When determining results from GWAS with a *p*-value ranging between 0.05 and 5×10^{-8}, other statistical approaches, rather than single standard significance may be beneficial.

Conclusion

Taking into account these considerations, a proportion of meta-analyses claimed statistical significance, but these results need to be interpreted with caution.

AUTO1-0111
GENETICS AND AUTOIMMUNITY

EXPRESSION OF HUMAN REG FAMILY GENES IN INFLAMMATORY BOWEL DISEASES AND ITS MOLECULAR MECHANISM

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Background

The pathophysiology of inflammatory bowel disease (IBD) reflects a balance between mucosal injury and reparative mechanisms. Some **re**generating **g**ene (*Reg*) family members have been reported to be expressed in Crohn's disease (CD) and ulcerative colitis (UC) and to be involved as proliferative mucosal factors in IBD. However, expression of all the *REG* family genes in IBD is still unclear.

Method

Here, we analyzed expression of all the *REG* family genes (*REG Iα*, *REG Iβ*, *REG III*, *HIP/PAP*, and *REG IV*) in biopsy specimens of UC and CD by real-time RT-PCR. *REG Iα*, *REG Iβ*, and *REG IV* genes were overexpressed in CD samples. *REG IV* gene was also overexpressed in UC samples. We further analyzed the expression mechanisms of *REG Iα*, *REG Iβ*, and *REG IV* genes in LS-174T and HT-29 human colonic epithelial cells.

Results

The expression of *REG Iα* was significantly induced by IL-6 or IL-22, and *REG Iβ* was induced by IL-22. Deletion analyses revealed that three regions (-220~-211, -179~-156, and -146~-130) in *REG Iα* and the region (-274~-260) in *REG Iβ* promoter were responsible for the activation by IL-22/IL-6. The promoters contain consensus transcription factor binding sequences for MZF1, RTEF1/TEAD4, and STAT3 in *REG Iα*, and HLTF/FOXN2F in *REG Iβ*, respectively. The introduction of siRNA for MZF1, RTEF1/TEAD4, STAT3, and HLTF/FOXN2F abolished the transcription of *REG Iα* and *REG Iβ*.

Conclusion

The gene activation mechanisms of *REG Iα/REG Iβ* may play a role in colon mucosal regeneration in IBD.

AUTO1-0143
IL-17, OTHER CYTOKINES AND AUTOIMMUNE INVOLVEMENT

GENE EXPRESSION OF BAFF, APRIL AND THEIR RECEPTORS IN LUPUS NEPHRITIS

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Background

BAFF and APRIL cytokines are crucial for the survival of B lymphocytes through the receptors BAFF-R, BCMA and TACI. Recent evidence (1, 2) show the importance of BAFF/APRIL in Lupus nephritis (LN) by demonstrating expression in glomeruli and tubular epithelial cells by immunohistochemistry. The aim of this study is to evaluate the relationship between gene expression of BAFF, APRIL and their receptors in urinary sediment compared with histological characteristics in patients with LN.

Method

Urine samples were collected from patients with SLE before renal biopsy. RNA extraction (High Pure RNA isolation kit-Roche), retrotranscription (Transcriber First Strand cDNA Synthesis –Roche-) and determination of gene expression by real-time PCR (FastStart Essential DNA Green Master -Roche Life Science-) were used for amplification of BAFF, APRIL and the three receptors (BAFF-R, TACI and BCMA).

Results

A total of 11 patients were evaluated. GAPDH was used as housekeeping gene. TACI and BAFF-R expression was found in 4 patients. Two of these patients also expressed APRIL. These patterns were not different according to pathological class (two patients had type IV LN, one patient had LN type I and one patient LN type V). The expression of APRIL was associated with the presence of cylinders in the sediment**.** No patient expressed urinary BAFF or BCMA, different to pathological expression.

Conclusion

Despite evidence of BAFF expression in the glomeruli by immunohistochemistry, BAFF gene expression was not demonstrated in the urinary sediment. Instead, BAFF-R, TACI and APRIL were found in patients with LN and urinary sediment with cellularity, epithelial cells and cylinders.

AUTO1-0668
IL-17, OTHER CYTOKINES AND AUTOIMMUNE INVOLVEMENT

P21 SUPPRESSES EXPERIENCED T CELLS BY CONTROLLING IFN-GAMMA PRODUCTION AND RESPONSES TO LOW AFFINITY ANTIGENS THROUGH MITOCHONDRIAL REGULATION IN AUTOIMMUNE T CELLS

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Background

T cells hyperactivation drives autoimmunity and systemic lupus erythematosus. We previously identified p21 as an autoimmunity suppressor. Although studies from our group and other laboratories addressed the p21 impact on T cells, the mechanism by which p21 directs its autoimmunity-suppressing effect remains a matter of debate. Here, we report an unknown p21 role in regulating the activation of experienced effector/memory T cells but not of naïve T cells, which is independent of its described cell cycle regulatory properties.

Method

After stimulation of preactivated T cells early activation indicators, including p-AKT, p-PKCq and p-p65, as well as NF-kB triggering, were increased in $p21^{-/-}$ compared to wild type (WT) T cells. The amplified T cell responses were linked to severely elevated IFN-gamma production, a cytokine that is closely linked to lupus development. In order to verify the relevance of these finding in autoimmunity we introduced the p21 deficiency in B6 lpr mice, which develop mild autoreativity.

Results

We found much higher IFN-gamma production in B6 p21-/- lpr mice, which was translated in acute lupus and early death. Enhanced activation and IFN-gamma production were linked to increased mitochondrial activity and mROS production Moreover, p21-/- T cells from TCR transgenic mice, specific for a low affinity antigen, responded much more intensely as compared to their normal counterparts.

Conclusion

Overall p21 appears to suppress T cell overactivation and autoimmunity by tempering mitochondrial activity. This effect controls early kinase activity and NF-kB activation and ultimately interferes with autoimmunity-associated features such as IFN-gamma production and responses to low affinity antigens.

AUTO1-0292
IL-17, OTHER CYTOKINES AND AUTOIMMUNE INVOLVEMENT

IN A HUMAN MYELOID CELL LINE BLYS GENE EXPRESSION IS INCREASED BY IFNA, WHILE BLYS PROTEIN RELEASE IS AFFECTED BY BOTH E2 AND IFNA

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Background

B Lymphocyte Stimulator (BLyS) is a key cytokine in the modulation of adaptive immunity and in the induction of autoimmunity. We evaluated *in vitro* effects of 17β-estradiol (E2) and Interferon α (hr-IFNα) on BLyS in a human myeloid cell line.

Method

U937 monocytes and U937-derived macrophages (50ng/mL PMA for 72 hours) were treated with E2 1nM, 10nM, 100nM or hr-IFNα 1000 IU/mL. Total RNA was extracted after 6, 24 and 48 hours; quantitative PCR was performed for *BLyS* gene, using *GAPDH* as reference. Data were analyzed with $2^{-\Delta\Delta Ct}$ method, and statistically evaluated with REST-384© using Pair Wise Fixed Reallocation Randomisation Test©. At the same time points BLyS protein release in culture supernatants was evaluated using a commercial ELISA kit; statistical analysis of BLyS protein data was performed with one-way ANOVA and Tukey's post hoc test, and unpaired t-test.

Results

E2 did not induce any modulation of *BLyS* gene expression (*p=n.s.*). hr-IFNα treatment induced an up-regulation of *BLyS*, faster and higher in derived-macrophages than monocytes (Fig.1). BLyS protein was constitutively released from both treated and untreated cells, yet in macrophage-derived cells, starting from 24 hours treatment, E2 induced soluble BLyS release at the highest doses, while IFNα blocked the release (Tab.1).

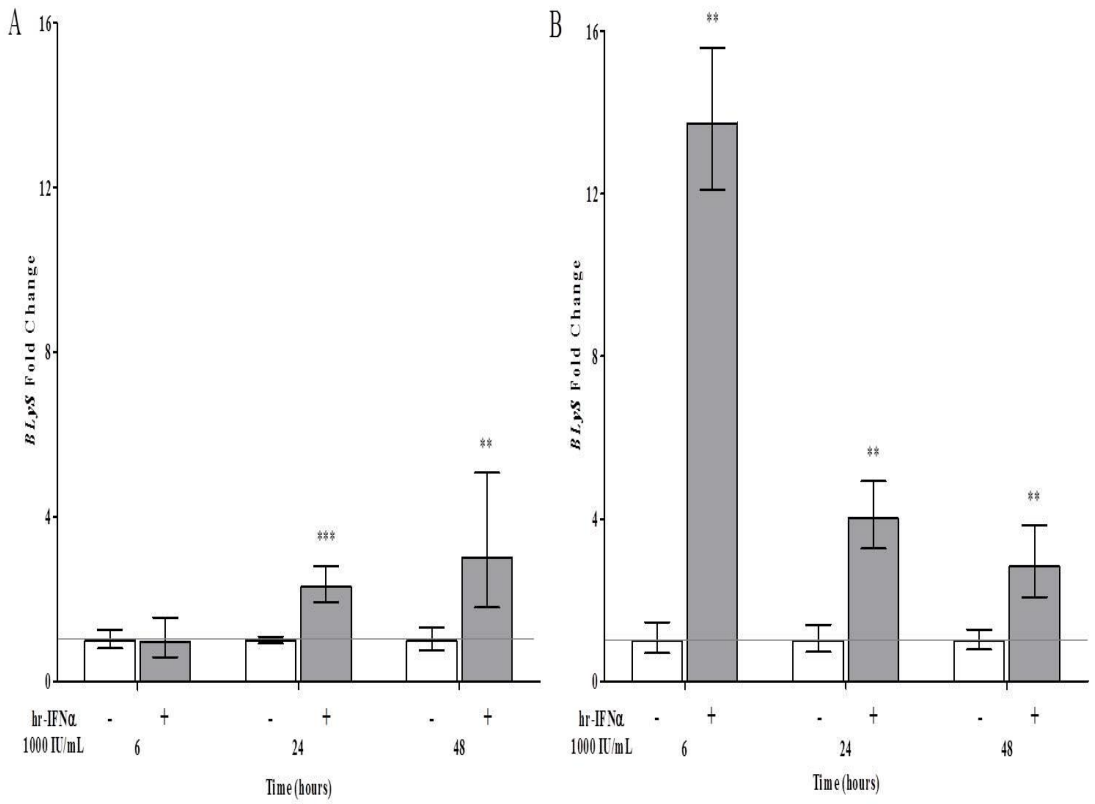

Fig. 1. Mean (min-max) fold changes of *BLyS* mRNA expression after 6, 24 and 48 hours of hr-IFNα treatment (+), in U937 monocytes (A) and U937-derived macrophages (B). Fold change = 1 was attributed, for each time point, to untreated cells (-), considered as controls. **p<0.01 ***p≤0.001.

U937	Medium	E2			IFNα
		1 nM	10 nM	100 nM	1000 IU/mL
6 h	209.36 (21.50)	201.73 (3.57)	224.57 (7.21)	191.68 (17.79)	153.76 (0.00)
24 h	1367.55 (50.17)	1355.73 (50.13)	1340.94 (29.22)	1270.26 (4.16)	1295.16 (51.85)
48 h	3153.03 (67.16)	3058.25 (129.52)	3102.46 (111.78)	3286.39 (175.21)	3514.33 (198.09)
ANOVA p-value	*< 0.0001****	*0.0001****	*< 0.0001****	*0.0002****	*0.0002****
U937+PMA					
6 h	79.78 (3.31)	86.53 (6.66)	84.19 (9.97)	67.86 (6.53)	70.88 (11.91)
24 h	405.19 (34.05)	760.55 (119.49)	715.22 (23.78)**	848.03 (76.37)*	88.02 (21.93)**
48 h	782.73 (15.97)	1465.35 (21.02)***	1486.18 (25.25)***	1343.92 (50.09)**	271.07 (38.45)**
ANOVA p-value	*0.0002****	*0.0007****	*< 0.0001****	*0.0004****	*0.0083***

Tab.1 BLyS expression in U937 and U937-derived macrophages (U937+PMA) treated with E2, at different concentrations, or hr-IFNα. Data represented are mean (Standard Deviation) of BLyS protein levels (pg/mL) in cell supernatants. Differences in soluble BLyS levels between untreated and treated cells at each time of culture, were analyzed by unpaired t-test. *p<0.05, **p<0.01, ***p≤0.001.

Conclusion

BLyS gene expression induced by IFNα, and BLyS protein release induced by E2, confirm the role of both IFNα and E2 in the modulation of adaptive immune response. Such effects seem to depend on cell phenotype, and suggest a major role of activated rather than resting cells in immunomodulation.

AUTO1-0715
IL-17, OTHER CYTOKINES AND AUTOIMMUNE INVOLVEMENT

GADD34 IS OVEREXPRESSED IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RELATED TO THE EXPRESSION OF TYPE I INTERFERON RESPONSE GENES

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Background

GADD34 (growth arrest and DNA damage-inducible protein 34) is a regulatory subunit of PP1 phosphatase which dephosphorylates eIF2α, representing a negative feedback loop of the unfolded protein response (UPR). Moreover, GADD34 is necessary for type I interferon (IFN) production in response to viral infection in murine models. We investigate here the expression of GADD34 in systemic lupus erythematosus (SLE), in which type I IFN has an important pathogenic role.

Method

We report a case-control study on GADD34 gene expression in PBMC of SLE patients (n=57) and age- and sex-matched healthy controls (n=30). The level of GADD34 gene expression, as well as IFNα and type-I IFN response genes in PBMC was measured by quantitative PCR.

Results

GADD34 gene expression was significantly higher in SLE patients compared with healthy controls ($p<0.001$), as well as the expression of another UPR gene, CHOP (CCAAT-enhancer-binding protein homologous protein) ($p<0.001$). No relation between UPR gene overexpression and lupus flares has been observed in our cohort of patients. Nevertheless, interestingly, GADD34 overexpression in PBMC of patients was related to the overexpression of IFNα ($p<0.001$) and type-I IFN response genes such as ISG15 ($p<0.001$) and IFIH1 ($p<0.001$).

Conclusion

These data point out the evidence of an unfolded protein response during the course of SLE and the relation between an UPR response and a type I IFN response in lupus patients.

AUTO1-0059
IL-17, OTHER CYTOKINES AND AUTOIMMUNE INVOLVEMENT

SERUM INTERLEUKIN 23 IN SYSTEMIC LUPUS ERYTHEMATOSUS – ASSOCIATION WITH LUPUS NEPHRITIS AND CARDIOVASCULAR RISK

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Background

Cytokine-mediated immunity plays a crucial role in the pathogenesis of various autoimmune diseases including systemic lupus erythematosus (SLE). The aim of this study was to evaluate association between serum levels of IL-23 and vascular involvement in SLE patients.

Method

Study was performed in 94 SLE patients and in 27 controls. Serum IL-23 was measured with ELISA using R&D Systems tests.

Carotid intima-media thickness and the presence of atherosclerotic plaques in carotid and lower extremities arteries were analyzed with B-mode ultrasound. Ankle-brachial and high resistance indeces were measured with Doppler ultrasonography.

We took into account classical cardiovascular risk factors, selected clinical manifestations and profile of autoantibodies.

Statistical analysis was performed with: chi^2Yates, chi^2Pearson, rank Spearman correlations tests, logistic regression analysis and multivariate stepwise analysis.**Results**

Concentrations of IL-23 significantly differed between SLE patients and the controls (p= 0.0005). Patients with high levels of IL-23 more frequently developed atherosclerosis showed as the presence of plaques in right common femoral artery (OR= 10.1; 95%CI:1.2-85.1) and lupus nephritis (OR= 3.2; 95%CI:1.1-9.6). Among classical atherosclerotic risk factors only obesity was significantly associated with IL-23 (OR= 3.8; 95%CI:1.2-12.3). Immunological characteristics significantly related to IL-23 were anti-phosphatidylethanolamine antibodies (OR= 12.7; 95%CI:1.5-108.1) and anti-SS-B antibodies (OR= 11.8; 95%CI:1.5-94.8). Association with anti-cardiolipin and anti-prothrombin antibodies was on the border of statistical significance (OR= 2.3; 95%CI:0.9-5.7 and OR= 8.4; 95%CI:1.0-71.1 respectively).

Conclusion

IL-23 may be involved in lupus nephritis pathogenesis. IL-23 through its significant association with obesity and antiphospholipid antibodies may promote hypercoagulable state contributing to atherothrombosis development in SLE patients.

AUTO1-0367
IL-17, OTHER CYTOKINES AND AUTOIMMUNE INVOLVEMENT

PERIPHERAL BLOOD MEMORY TH17 SUBSETS IN PATIENTS WITH CHRONIC AND ACUTE SARCOIDOSIS

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Background

Sarcoidosis is considered the archetype of immune granulomatous disorder, since immunoregulatory mechanisms and characterized by peripheral blood (PB) T cell lymphopenia and disturbances in T-helper (Th) subsets ratio such as Treg-vs.-Th17 and Th1-vs.-Th17.

Method

To analyze the frequency of Th subsets, PB from were 26 healthy controls (HC) and 46 patients with chronic sarcoidosis (CS) and 11 acute sarcoidosis (AS) was evaluated by multicolor flow cytometry. Diagnosis of sarcoidosis was determined according to criteria of disease, clinicoradiological findings and histological evidence showing noncaseating epithelioid cell granulomas. All patients were without immunosuppressive treatment. Based on the expression of CCR4, CCR6, CXCR3, CXCR5 in CD45RA-negative cell main Th subsets were identified.

Results

The percentage of CXCR5-CXCR3-CCR6+CCR4+ Th (Th17 and Th22 subsets) was significantly higher in CS (14.54% (11.45; 16.63)) than in AS and HC (10.62% (8.86; 14.62) and 11.43% (9.68; 14.07), p=0.023 and p=0.028, respectively). So-called double-positive Th17 (CXCR5-CXCR3+CCR6+CCR4+) were higher in CS and AS in comparison with HC (14.22% (10.41; 17.82) and 17.21% (11.37; 18.77) vs 10.82% (8.68; 12.47), p<0.001 and p=0.001, respectively). While the relative number of Th1 (CXCR5-CXCR3+CCR6-CCR4-) was significantly decreased only in CS vs HC (11.23% (8.67; 16.30) vs 15.90% (12.28; 21.09), p=0.008). No differences between the groups were observed in relative number of double-negative Th17 (CXCR5-CXCR3-CCR6+CCR4-) and Th1/Th17 (CXCR5-CXCR3+CCR6+CCR4-) subsets within CD45RA-negative Th cells.

Conclusion

Disturbance in Th1 and Th17 found in PB from CS and AS can help to design new immunological biomarkers characterizing the immunopathogenesis of sarcoidosis and to find alternative methods for the future treatment of sarcoidosis.

AUTO1-0608
IMMUNE DEFICIENCY AND AUTOIMMUNITY

ISOLATED IGG SUBCLASS DEFICIENCY: A LINK BETWEEN PRIMARY IMMUNODEFICIENCY AND AUTOIMMUNITY

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Background

Isolated decreased serum-immunoglobulin G subclasses are associated with severe and/or recurrent infections. However, the prevalence of other clinical problems including allergy and autoimmune diseases has been poorly described.

Method

We studied IgG subclass deficiency according to the diagnostic criteria of the European Society for Immunodeficiencies (ESID) (recurrent or severe bacterial infections AND normal IgG, A and M serum/plasma levels AND low levels in one or more IgG subclass AND normal IgG antibody response to some vaccinations AND exclusion of T cell defect) by reviewing the charts and analyzing retrospectively patients diagnosed in a large teaching hospital in Madrid.

Results

A total of 93 cases from our cohort were evaluated (Women 70, 75.3%, mean age 46, range 16-85 years). Distribution of IgG subclass deficiencies was: IgG1 (12.9%), IgG2 (9.7%), IgG3 (7.5%), IgG4 (45.2%), more than one decreased IgG subclass (24.7%). Our main finding is that in addition to infections, 38 (40.9%) of patients had a history of an inflammatory or autoimmune condition. Age, sex and type of IgG subclass deficiency were not significantly associated with the presence of an autoimmune or inflammatory condition.

Conclusion

Our results illustrate the clinical challenge of defining a high prevalence of autoimmune diseases among patient with IgG subclass deficiency. Although this high prevalence of autoimmune diseases in IgG subclass deficient patients may reflect the skewed tertiary center population studied, it should be taken into account for the proper management of these patients. A larger cohort of patients is needed to explore fully its clinical consequences.

AUTO1-0932
IMMUNE DEFICIENCY AND AUTOIMMUNITY

ADRENAL STEROIDS IN RHEUMATOID ARTHRITIS

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Background

Several lines of evidence indicate that hormonal factors play an important role in the complex pathogenesis of rheumatoid arthritis (RA). Among various hormones, major attention has been focused on adrenal steroids, especially glucocorticoids (GC) as the final products of the hypothalamic- pituitary-adrenal axis (HPA), but also adrenal androgens, such as dehydroepiandrosterone (DHEA), its sulphate (DHEAS) and androstenedione.

Method

Aim of the study was to review current data on serum adrenocortical steroids and its response to ACTH in patients with RA. To assess their relationship to the disease activity. To find some genetic markers of adrenocortical insufficiency in RA patients

Results

Subtle differences in HPA axis function were found between RA patients versus controls and some studies demonstrated an insufficient cortisol secretion to counteract the circadian fluctuation of inflammatory cytokines and clinical symptoms. In our study patients with RA and higher disease activity score (DAS28 > 3.2) had significantly lower serum cortisol, DHEAS and androstenedione compared to healthy controls ($P > 0.05$ for all hormones). They also had significantly lower response of DHEAS as well as cortisol after ACTH administration. Among 448 RA patients we demonstrated a significant effect of polymorphisms in ZKSCAN5 and ARPC1A genes on DHEAS levels in female RA subjects but not in control group.

Conclusion

We conclude that patients with RA have subtle adrenocortical insufficiency not only in GC but also in adrenal androgen production and activity. Polymorphisms of ZKSCAN5 and ARPC1A genes may contribute to lower DHEAS in these subjects.

AUTO1-0485
IMMUNE DEFICIENCY AND AUTOIMMUNITY

CLINICAL FEATURES AND OPTIONS OF TREATMENT OF CHILDREN WITH PI(3)KCD DEFECT

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Background

Activated PI3K syndrome is a combined immunodeficiency with different severe infections, lymphoproliferative syndrome, autoimmune complication and high risk oncological disease.

Method

The current study included 5 patients (4-13 years old) from different families with the age of onset from 2 months to 12 years. Three patients had activated heterozygous mutation E1021K, one – H502R (not referenced in the database) in PI(3)cd, one patient - c.1425+1G-C in PI(3)KR1. The lymphoproliferative syndrome included lymphadenopathy (5/5), hepatomegaly (3/5), splenomegaly (3/5). Other complications: colitis – 3/5, nephritis 2/5, endobronchitis – 1/5, autism – 1/5, EBV-associated diffuse B-cell's lymphomas – 1/5. Infections - 4/5. EBV viremia – 5/5. Hypogammaglobulinemia 4/5, hyper-IgM – 3/5, decrease memory B cell – 4/5, decrease naïve CD4+ 4/5. Four patients received antimicrobial therapy, regular IVIG therapy. All patients was treated of Rituximab.

Results

during a 6-12 months period 3 patients received Sirolimus as initial therapy, one patient previously was treating with corticosteroids, cyclosporine, mycophenolate mofetil, tacrolimus, one patient didn't have specific therapy (treated for lymphoma). Efficacy was assessed on a 5 point scale for complications.
Treatment with Jak-kinase inhibitors (Ruxolitinib), Tofacitinib) was started in two patients due to insufficient response to initial therapy. One patient with good result to Sirolimus. HCST was performed for two patient (one - died of post-transplant complications, one – alive (follow up about 10 months).

Conclusion

Targeted immunosuppressive therapy can be considered as a curative treatment for patient's with PI(3)k. In case of severe disease with poor response to pharmacological treatment or malignancy, bone marrow transplantation is indicated.

AUTO1-0038
IMMUNE DEFICIENCY AND AUTOIMMUNITY

CHIKUNGUNYA VIRUS AND AUTOIMMUNITY.

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Background

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus. Fever, rash and severe arthralgia are the hallmarks of chikungunya fever(CHIKF). The acute course of the disease lasts few weeks to months. Chronic, persistent arthritis has been described mimicking rheumatoid arthritis (RA), requiring immunosuppressive drugs.

The purpose of this presentation is to characterize the chronic clinical course of CHIKF associated arthritis and it's immunological pathogenic mechanisms.

Method

The current literature was reviewed.

Results

Recently, the burden of post-epidemic chronic persistent rheumatic course on the functional status of affected individuals, comprising large populations has been studied. A third of affected individuals had persistent pain months to years post epidemic and the identified risk factors for functional disability were determined.

Inflammatory biomarkers such as interleukin 6, and relevant chemokines have been found to correlate with the severity of post-epidemic chronic disease. There are conflicting reports on ANA as well as RF and ACPA positivity during infections.

In a recent report, 8 out of 10 -infected individuals developed chronic persistent rheumatic course and met classification criteria for RA.

These 8 patients, as in RA patients had a greater percentage of activated and effector CD4+ and CD8+ T cells than healthy controls.
Recently, a patient with CHIKF developed SLE (unpublished data).

Conclusion

CHKV infections may have a chronic persistent course, overlapping clinical and immunologic features with RA.

In the appropriate setting CHIKV infection should be considered in a patient with a new symmetric polyarthritis.

In a genetically- prone individual, in a particular environmental and infectious setting, like CHIKF outbreak, an autoimmune disease can emerge.

AUTO1-0094
IMMUNO-MEDIATED GLOMERULOPATHIES

DIFFERENT CUT-OFFS FOR RENAL RESISTIVE INDEX REFLECT RENAL AND OTHER ORGAN INVOLVEMENT AND PREDICT WORSENING IN SYSTEMIC SCLEROSIS (SSc) PATIENTS

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Background

Renal Resistive Index(RRI) reflects changes in renal vascular and tubular-interstitial compartments and systemic vascular compliance. As RRI>0.70 cut-off may underestimate renal injury in younger decades, our study aimed at describing RRI in our SSc population, testing both>0.70 RRI cut-off and SSc-age-adjusted cut-offs in reflecting different organ involvements, finally analysing the prognostic value of RRI for SSc-related worsening.

Method

SSc patients classified through ACR/EULAR 2013 criteria,≥18 years were enrolled after informed consent. Data on laboratory, instrumental and therapeutic features were retrospectively collected. SSc-age-adjusted pathologic cut-offs were created clustering in age quartiles and considering RRI values>75th percentile as pathologic (Table 1A).

Clinical worsening was defined in case of any event listed in Table 1B.

A

Age-SSc adjusted pathologic RRI cut-offs	
Age	Pathologic RRI
1° quartile ≤ 49	≥0.68
2° quartile 50-59	≥0.70
3° quartile 60-69	≥0.75
4° quartile ≥70	≥0.78

B

Definitions of worsening
a) Skin worsening as an increase of mRSS≥5 units in two consecutive visits b) Peripheral vascular worsening as the appearance of new digital ulcers or the worsening of nailfold videocapillaroscopy scleroderma pattern c) Lung worsening as decline of FVC≥15% or FVC<80% with new detection of ILD on chest HRCT or worsening of HRCT-ILD extent d) Cardiac worsening as new onset of left ventricular failure requiring treatments or new onset of PAH confirmed on RHC or detection of severe ventricular arrhythmias on 24h EKG e) Renal worsening as a new scleroderma renal crisis or reduction of creatinine clearance ≤ 30 ml/min. f) Death

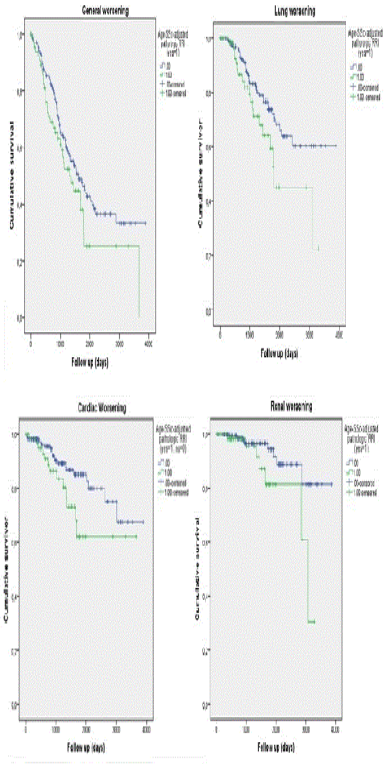
Results

In 250 SSc patients(mean disease duration 7.2±8.3years), RRI showed significant correlations with age(ρ=0.56,p<0.001) and creatinine clearance(ρ=-0.38,p<0.001), as well as significant associations with general population RRI determinants. While RRI absolute value and 0.70 cut-off were related with comorbidities, renal function, and few SSc-related features, our SSc-age-adjusted RRI cut-offs could not detect early renal damage but were significantly associated with various disease related skin and lung fibrotic manifestations, as well as vasculopathic complications(Table 2A). After a mean 3.6±2.6 years follow-up, only SSc-age-adjusted RRI cut-offs were significantly predictive for cardiac, lung and renal worsening(Table 2B).

2A	Study Population (250 pts)	Study population analyses of mean RRI values (250 pts)			RRI ≥ 0,70 pathologic cut-off					Proposed Age- and SSc-adjusted pathologic RRI cut-offs				
					RRI ≥ 0,70 (113 pts)		RRI <0,70 (137 pts)			Pathologic RRI (72 pts)		Non Pathologic RRI (178 pts)		
		present	absent	p value	n	%	n	%	p value	n	%	n	%	p value
Arterial Hypertension (n, %)	86 (34,4%)	0,72 ± 0,07	0,67 ± 0,06	**<0,001***	56	49,56%	30	21,90%	**<0,001***	34	47,22%	52	29,21%	**0,007***
Diabetes Mellitus (n, %)	10 (4,0%)	0,74 ± 0,06	0,69 ± 0,07	**0,009***	9	7,96%	1	0,73%	**0,004***	3	4,17%	7	3,93%	N.S.
Hyperuricaemia (n, %)	20 (8,0%)	0,75 ± 0,08	0,68 ± 0,07	**<0,001***	15	13,27%	5	3,65%	**0,006***	12	16,67%	18	10,11%	**0,022***
Skin subset: no skin involvement/limited/diffuse (n, %) - missing data 3	75 (30,0%) / 131 (52,4%) / 41 (16,4%)	0,67 ± 0,06	0,69 ± 0,07	**0,026***	30	26,55%	45	32,85%	N.S.	46	63,89%	85	47,75%	**<0,001***
mRSS (median, range)	2 (0-38)	Spearman ρ=0,017		N.S.	4,45 ± 6,98		5,06 ± 8,30		N.S.	6,70 ± 7,64		4,12 ± 7,69		**0,027***
Fulfillment of VEDOSS criteria without other SSc features (n, %)	57 (22,8%)	0,68 ± 0,06	0,69 ± 0,07	N.S.	22	19,47%	35	25,55%	N.S.	8	11,11%	49	27,53%	**0,008***
History/Current Digital Ulcers (n, %)	80 (32,0%)	0,69 ± 0,07	0,68 ± 0,07	N.S.	45	39,82%	35	25,55%	N.S.	31	43,06%	49	27,53%	**0,028***
Nailfold Videocapillaroscopy scleroderma pattern (absent/aspecific/early/active/late) - missing data 28	3 (1,2%) / 31 (12,4%) / 67 (26,8%) / 71 (28,4%) / 50 (20,0%)	0,71 ± 0,07	0,68 ± 0,07	**0,003***	28	24,78%	22	16,06%	**0,046***	22	30,56%	28	15,73%	**0,050***
Telangectasias (n, %)	24 (9,6%)	0,69 ± 0,08	0,68 ± 0,06	N.S.	10	8,85%	14	10,22%	N.S.	9	12,50%	15	8,43%	**0,052***
Systolic PAP on Echo (median, range)	25 (10-93)	0,73 ± 0,06	0,68 ± 0,07	**<0,001***	30,12 ± 11,75		24,68 ± 5,60		**<0,001***	29,63 ± 9,70		26,15 ± 8,97		**0,016***
Diastolic Dysfunction (E/A<1) (n, %)	75 (30,0%)	0,70 ± 0,06	0,67 ± 0,06	**0,002***	42	37,17%	33	24,09%	**0,009***	23	31,94%	60	33,71%	N.S.
Interstitial Lung Disease (n, %)	91 (36,4%)	0,69 ± 0,08	0,69 ± 0,07	N.S.	44	38,94%	47	34,31%	N.S.	37	51,39%	54	30,34%	**0,002***
FVC (%, median, range)	106 (31-162)	Spearman ρ=-0,009		N.S.	103,59 ± 20,76		106,75 ± 22,27		N.S.	99,79 ± 21,90		107,58 ± 21,130		**0,010***
DLCO (%, median, range)	73 (23-133)	Spearman ρ=-0,198		**0,002***	69,82 ± 21,17		75,53 ± 18,80		**0,027***	66,99 ± 20,19		75,35 ± 19,58		**0,003***
Dyspnoea NYHA class ≥2 (n, %)	105 (42%)	0,70 ± 0,07	0,68 ± 0,07	**0,030***	54	47,79%	50	36,50%	N.S.	38	52,78%	67	37,64%	**0,029***
ESR increase (n, %)	34 (13,6%)	0,72 ± 0,07	0,67 ± 0,07	**<0,001***	34	30,09%	29	21,17%	0,051	26	36,11%	36	20,22%	**0,003***
CRP increase (n, %)	62 (24,8%)	0,71 ± 0,07	0,68 ± 0,07	0,087	18	15,93%	16	11,68%	N.S.	14	19,44%	20	11,24%	**0,067***
Anti-Centromere antibody positivity (n, %)	141 (56,4%)	0,69 ± 0,07	0,68 ± 0,07	N.S.	66	58,41%	75	54,74%	N.S.	37	51,39%	108	60,67%	**0,037***
Anti-Topoisomerase I antibody positivity (n, %)	68 (27,2%)	0,69 ± 0,07	0,69 ± 0,07	N.S.	32	28,32%	36	26,28%	N.S.	30	41,67%	38	21,35%	**<0,001***
NTproBNP (median, range)	114 (12-3580)	Spearman ρ=0,232		**0,037***	343,56 ±604,46		160,51 ± 208,82		**0,005***	218 (12-1455)		85 (15-3580)		**< 0,001***
Cockcroft-Gault calculated Creatinine Clearance (median, range)	83,4 (19,3-191,5)	Spearman ρ=-0,345		**<0,001***	79,28 ± 28,04		95,83 ± 29,80		**<0,001***	87,36 ± 32,80		88,70 ± 29,04		N.S.
Sildenafil (n, %)	45 (18,0%)	0,71 ± 0,07	0,68 ± 0,07	0,056	25	22,12%	20	14,60%	N.S.	19	26,39%	26	14,61%	**0,028***
Bosentan (n, %)	42 (16,8%)	0,70 ± 0,68	0,68 ± 0,07	N.S.	24	21,24%	18	13,14%	0,088	20	27,78%	22	12,36%	**0,003***
Statins (n, %)	25 (10,0%)	0,72 ± 0,06	0,68 ± 0,07	**0,006***	16	14,16%	9	6,57%	**0,046***	6	8,33%	19	10,67%	N.S.
Diuretics (n, %)	21 (8,4%)	0,74 ± 0,07	0,68 ± 0,07	**<0,001***	16	14,16%	5	3,65%	**0,003***	12	16,67%	9	5,06%	**0,003***
Sartans (n, %)	25 (10,0%)	0,72 ± 0,08	0,68 ± 0,07	**0,017***	15	13,27%	10	7,30%	N.S.	11	15,28%	14	7,87%	0,077
Beta-blockers (n, %)	15 (6,0%)	0,73 ± 0,06	0,68 ± 0,07	**0,006***	11	9,73%	4	2,92%	**0,031***	9	12,50%	6	3,37%	**0,006***
ACE-inhibitors (n, %)	43 (17,2%)	0,72 ± 0,06	0,68 ± 0,07	**0,001***	29	25,66%	14	10,22%	**0,001***	19	26,39%	24	13,48%	**0,014***

* = statistically significant with p<0,05

2B	Study population (250 pts)		Study population analyses of mean RRI values (250 pts)		RRI ≥ 0,70 pathologic cut-off (113 pts)			Proposed Age- and SSc-adjusted pathologic RRI cut-offs (72 pathologic pts)		
	n	%	IRR medio ± DS	p value	n	%	p value	n	%	p value
General worsening	119	47,60%	0,69 ± 0,08	N.S.	51	45,13%	N.S.	37	51,39%	0,097
Death	15	6,00%	0,71 ± 0,10	N.S.	9	7,96%	N.S.	6	8,33%	N.S.
Skin worsening	16	6,40%	0,68 ± 0,07	N.S.	5	4,42%	N.S.	6	8,33%	N.S.
Vascular worsening	57	22,80%	0,69 ± 0,07	N.S.	23	20,35%	N.S.	16	22,22%	N.S.
Cardiac worsening	35	14,00%	0,71 ± 0,08	0,075	19	16,81%	N.S.	13	18,06%	**0,045**
Lung worsening	55	22,00%	0,70 ± 0,08	N.S.	27	23,89%	N.S.	19	26,39%	**0,034**
Renal worsening	15	6,00%	0,72 ± 0,07	0,078	8	7,08%	N.S.	7	9,72%	**0,026**



Conclusion

In clinical practice, different age-SSc-adjusted or non-adjusted RRI cut-offs may be used to evaluate renal and extrarenal involvement, resembling DLCO for parenchymal and vascular lung involvement. These RRI cut-offs may be considered as possible predictors of kidney, lung and cardiac worsening in SSc patients.

AUTO1-0224
IMMUNO-MEDIATED GLOMERULOPATHIES

EMERGING EVIDENCE FOR THE ACQUISITION OF A ROBUST PRO-INFLAMMATORY PHENOTYPE BY THE HUMAN RENAL GLOMERULAR ENDOTHELIAL CELLS IN JUVENILE-ONSET LUPUS NEPHRITIS

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Background

Lupus nephritis (LN) is a chronic inflammatory kidney disease affecting up to 80% of young lupus patients and causing severe renal damage. The native kidney cells' role in LN remains widely unknown. Therefore, this study focused on investigating the response of the renal glomerular endothelial cells (GEnCs) to various LN-associated pro-inflammatory stimuli, by developing an *in vitro* culture model.

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Method

A human cell line of conditionally immortalised GEnCs (ciGEnCs) was used. ciGEnCs were treated for 24 hours with various cytokines (10 ng/ml) upregulated in the plasma of patients with active LN. The effect of bacterial endotoxin inflammation was examined using LPS (1 μg/ml). The secretion of a panel of pro-inflammatory cytokines (IL-6, IL-10, TNF-α, IFN-γ), chemokines (MCP-1, MIP-1α, IP-10) and growth factors (M-CSF, GM-CSF) was tested via Luminex ELISA. Adhesion molecule (ICAM-1, VCAM-1) and cytokine receptor (IL1-RI) surface expression were examined using flow cytometry. GEnC viability was tested through Annexin/PI staining and flow cytometry. Data were analysed by Kruskal-Wallis/Friedman test with Dunn's post-hoc test. All measurements were compared to those of the untreated ciGEnCs.

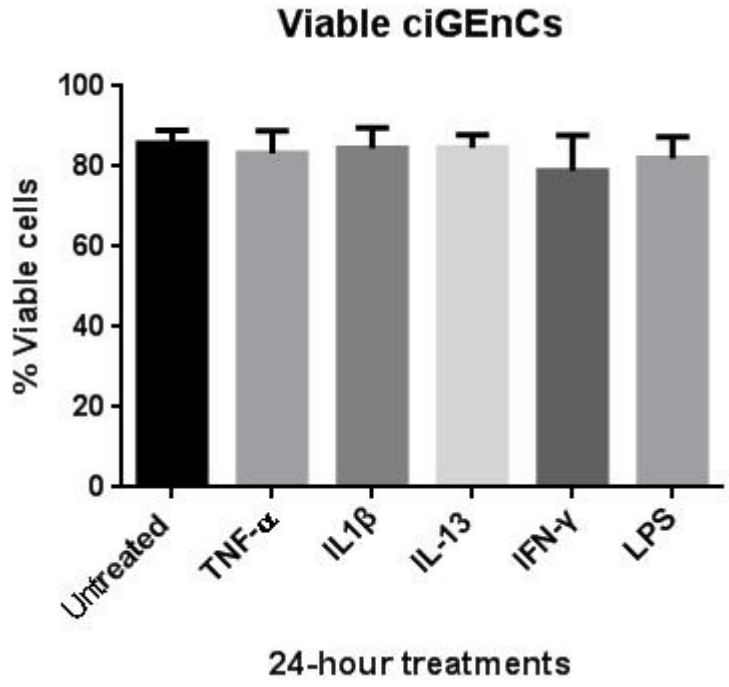
Results

Four cytokines - TNF-α, IL-1β, IL-13, IFN-γ - and LPS, are responsible for the *in vitro* GEnC activation at 24 hours. They potently stimulate the ciGEnCs to produce a variety of pro-inflammatory cytokines, chemokines, growth factors, adhesion molecules and cytokine receptors (**Table1**). Over 75% of ciGEnCs retained their viability, indicating that GEnC activation, not GEnC death, induced their pro-inflammatory phenotype (**Figure1**).

Table1

Pro-inflammatory proteins	ciGEnCs	
MCP-1	**Untreated** (800.1 pg/ml; [446-1705])	**TNF-α/IL-1β** **(3755 pg/ml; [3359-3911]) **LPS** *(2876 pg/ml; [2637-2984])
MIP-1α	**Untreated** (208.5 pg/ml; [207-209])	**TNF-α** *(222.3 pg/ml; [221-223.3]) **IL-1β** *(221.5 pg/ml; [215.8-225.8]) **LPS** *(225.8 pg/ml; [219.1-229.5])
IP-10	**Untreated** (0.514 pg/ml; [0.370-0.610])	**IFN-γ** **(3015 pg/ml; [2642-311]) **LPS** *(2870 pg/ml; [1042-3147])
IL-6	**Untreated** (30.55 pg/ml; [16.9-108.5])	**IL-1β** ***(3479 pg/ml; [1815-5243]) **LPS** ***(3323 pg/ml; [2083-4886])
IL-10	**Untreated** (0.514 pg/ml; [0.370-0.610])	**IFN-γ** **(18.19 pg/ml; [15.69-19.77]) **LPS** **(17.32 pg/ml; [9.014-20.25])
sVCAM-1	**Untreated** (0.51 pg/ml; [0.32-0.44])	**IL-13** *(25.15 pg/ml; [23.4-26.8])
GM-CSF	**Untreated** (0 pg/ml; [0-0])	**TNF-α** *(197.7 pg/ml; [189.7-272.3]) **IL-1β** *** (950.5 pg/ml; [464.9-1128]) **LPS** *(312.2 pg/ml; [125.5-576.5])
TNF-α	**Untreated** (4.484 pg/ml; [3.717-4.383])	**IL-1β** *(10.60 pg/ml; [7.048-12.71]) **IFN-γ** *(8.381 pg/ml; [7.270-8.825]) **LPS** *** (14.60 pg/ml; [10.38-20.15])
IFN-γ	**Untreated** (0 pg/ml; [0-0])	**LPS** **(28.47 pg/ml; [12.14-40.44])
VCAM-1	**Untreated** (MFI: 59.60; [49.65-69.58])	**TNF-α/IL-13** ***(MFI:119; [85.13-163.3])
ICAM-1	**Untreated** (MFI: 1872; [1625-2932])	**TNF-α** *(MFI: 10350; [7581-13287]) **IL-1β** **(MFI: 6727; [6397-11247]) **LPS** **(MFI: 8457; [6381-12939])
IL-1RI	**Untreated** (MFI: 21.5; [13.28-24.95])	**LPS** *(MFI: 28.4; [17.6-40.2])

Figure1



Conclusion

This study provides evidence for a key role for the human GEnCs in LN inflammation.

AUTO1-0014
IMMUNO-MEDIATED GLOMERULOPATHIES

β2-GLYCOPROTEIN I/IgA IMMUNE COMPLEXES A MARKER TO PREDICT THROMBOSIS AFTER RENAL TRANSPLANTATION IN PATIENTS WITH ANTIPHOSPHOLIPID ANTIBODIES

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Background

The presence of circulating immune complexes of IgA bound to β 2 -glycoprotein I (B2A-CIC) has been associated with occurrence of acute thrombotic events. In this work we study its possible predictive value for the appearance of acute thrombotic events in patients who are going to undergo transplant surgery, a well-known trigger of acute thrombotic events in aPL carriers.

Method

A follow-up study based on the Magnum 12+12 Cohort of patients who received a kidney transplant (n=1339). Three groups were established: group 1 patients who were positive for IgA anti-β 2 - glycoprotein I (aB2GP1) and B2A-CIC (n=125); group 2 patients who were positive only for IgA aB2GP1 (n=240); and control group, patients who were negative for IgA aB2GP1 (n=974). Levels of autoantibodies and B2A- CIC were quantified immediately before the transplant surgery and patients were followed up for 6 months.

Results

In group 1, 46.4% of patients experienced any type of thrombosis versus 10.4% in group 2 ($P<0.001$) and 8.6% in the control group ($P<0.001$). The incidence of graft thrombosis in group 1 (31.2%) was significantly higher than that observed in group 2 (3.3%, $P<0.001$) and the control group (2.6%, $P<0.001$). In a multivariate analysis, the presence of B2A-CIC was an independent variable to experience any type of posttransplant thrombosis (hazard ratio, 6.72; 95% confidence interval, 4.81–9.37) and, prominently, for graft thrombosis (hazard ratio, 14.75; 95% confidence interval, 9.11–23.89). No significant differences were found between B2A-CIC–negative and control group patients.

Conclusion

The presence of B2A-CIC is a predictor of acute thrombotic events.

AUTO1-0867
IMMUNO-MEDIATED GLOMERULOPATHIES

SAFETY OF OUTPATIENT PERCUTANEOUS NATIVE RENAL BIOPSY IN SYSTEMIC AUTOIMMUNE DISEASES: RESULTS FROM A MONOCENTRIC COHORT

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Background

To investigate the safety of performing percutaneous native kidney biopsy (PKB) as an outpatient procedure (implying an observation period of 6 hrs) compared to the traditional inpatient policy in patients with systemic autoimmune conditions.

Method

Group I, in whom PKB was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom PKB was performed and followed by at least 1-day hospital admission. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000-November 2012 as in patient procedure. All biopsies were performed by a single nephrologist following a structured protocol.

Results

Out of 462 biopsies reviewed, a total of 81 biopsies (group I and group II) were included in this study, 44 (54%) of patients were female and the mean age was 49.9 ± 17.6 years. Twenty-six per cent of biopsies were performed for the diagnostic workup of nephrotic range proteinuria, 21% for rapidly progressive renal insufficiency, and the remaining 53% for non-nephrotic proteinuria and/or hematuria. No patient suffered for a major complication and only 3 (3.7 %) patients developed a minor complication, including gross hematuria in one case and subcapsular perinephric hematoma on sonography not requiring intervention in 2 patients

Conclusion

The lack of major complications and the very limited rate of minor bleeding support that outpatient biopsy could be a valuable, safe, and potentially cost-effective method of obtaining diagnostic renal tissue in patients with systemic autoimmune diseases.

AUTO1-0879
IMMUNO-MEDIATED GLOMERULOPATHIES

CYCLOPHOSPHAMIDE-SPARING ROLE OF AN INTENSIFIED B-CELL DEPLETION PROTOCOL IN ANCA-ASSOCIATED VASCULITIS: A CASE-CONTROL STUDY

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Background

The management of ANCA-associated-vasculitis (AAV) requires the use of immunosuppressive drugs with potential toxicity. Recently, two trials demonstrated the efficacy of Rituximab (RTX) for the therapy of AAV.
This case-control study aims to evaluate the immunosuppressive-sparing effect of a RTX-based protocol compared to the standard cyclophosphamide (CYC) treatment.

Method

26 patients with AAV and necrotising extracapillary glomerulonephritis were prospectively enrolled. Thirteen patients received an intensified protocol of B-cell depletion therapy (IBCDT) consisting of 4-weekly infusions of 375 mg/m2 RTX followed by 2 infusions after 1 and 2 months, 3 pulses of methylprednisolone followed by prednisone tapered to 5 mg/day in three months and 2 pulses of 10 mg/kg CYC, without further maintenance therapy Thirteen patients treated with 2 mg/kg/day CYC followed by azathioprine as a maintenance therapy served as controls

Results

A significant improvement ($p<0.05$) of B-VAS, ESR, CRP and ANCA was observed in the IBCDT-group at 3, 6 and 12 months, with decrease of mean creatinine values from 4.81±6.4 mg/dl to 2.21±3.8 mg/dl.

When compared to controls, no difference was observed in terms of complete and partial response. However, the IBCDT regimen achieved a 1g/month reduction of CYC cumulative dose ($p<0.001$).

Conclusion

In the treatment of this sample of severe AAV patients, the IBCT protocol appeared to be non inferior to CYC-based regimen. Notably, the IBCDT regimen allowed a significant reduction of CYC cumulative dose.

AUTO1-0930
IMMUNO-MEDIATED GLOMERULOPATHIES

PROGNOSIS OF SCLERODERMA RENAL CRISIS IN PATIENTS TREATED WITH PLASMA EXCHANGE: A MONOCENTRIC EXPERIENCE

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Background

Scleroderma renal crisis (SRC) is a rare but severe complication of systemic sclerosis (SSc) and evolves into endstage renal disease (ESRD) in many cases. The aim of the study was to evaluate the outcome effects of treatment with plasma-exchange (PEx) on SRC-SSc.

Method

In the last 20 years, 23 SSc patients followed in our Rheumatology Unit developed SRC. Clinical features are summarized in the Table. We reviewed their clinical records, evaluating the patient outcomes after 1 year and the survival after 5 yrs. SRC was treated in all cases with increasing doses of ACE-inhibitors. In 13 patients PEx was performed in addition to pharmacological treatment; the main indication was a concomitant microangiopathy. PEx treatment duration ranged between 1 and 10 months (mean number of sessions per patient 26 ± 11).

Table. Clinical features of SRC-SSc patients

	SRC-SSc patients
Female gender, n (%)	16 (69.6)
Age at SRC onset (mean±SD, yrs)	49.6±12.9
SSc duration (mean±SD, yrs)	3.9±4.6
Diffuse cutaneous form, n (%)	19 (82.6)
ANA, n (%)	23 (100)
Anti-topoisomerase I, n (%)	2 (8.7)
Anti-centromere, n (%)	9 (39.1)
Anti-RNA polimerase III, n (%)	12 (52.2)

Results

In the first year after SRC onset 13 of 23 patients (56.5%) developed ESRD and 6 of them died due to SRC complications (26.1%). Eight patients treated with PEx preserved sufficient renal function to avoid dialysis and 5 developed ESRD; 1 died because of SRC complications. Only two patients treated with ACE-inhibitors avoided dialysis, 8 developed ESRD; 5 died because of SRC complications. The 5-year cumulative survival evaluated in 20 SSc patients was 70% in the group treated with PEx and 10% in that treated only with ACE-inhibitors. The other 3 patients reached now 2 yrs of follow-up.

Conclusion

Although long-term prognosis of SRC remains disappointing, PEx seems able to improve the outcome of SRC-SSc.

AUTO1-0758
INFECTION AND AUTOIMMUNITY

ANTIBODIES DIRECTED AGAINST BACTERIAL ANTIGENS IN SERA OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background

Primary biliary cholangitis (PBC) is a cholestatic, autoimmune liver disease. We studied the role of environmental agents in the pathogenesis of PBC and the aim of the work was to determine the level of antibodies directed against bacterial antigens in sera of patients with PBC. We detected anti-*Chlamydia pneumoniae* (anti-*Cpn*), anti-*Yersinia enterolitica,* anti-*Helicobacter pylori* (anti-*Hp*) and anti- *Mycoplasma pneumoniae* (anti- *Mycoplasma p.*) antibodies. We studied in vitro the influence of the bacterial peptide on specific binding antigen-antibody.

Method

Anti-*Cpn,* anti-*Yersinia enterolitica,* anti-*Hp* and anti- *Mycoplasma p.*antibodies were determined by ELISA kit in 92 PBC and 92 control patients (other liver diseases, healthy controls).

Results

Seroprevalence of anti-*Cpn,* anti-*Yersinia enterolitica,* anti-*Hp* and anti-*Mycoplasma p.* antibodies in PBC group was significantly higher than those in pathological and healthy control and was: 74%, 40%, 84% and 39% respectively. The odds ratios (ORs) of the presence of anti-bacterial antibodies for the PBC patients versus the healthy control were 3.89 (95% CI 1.4-10.4). The mean level of of anti-*Cpn* in PBC group was significantly higher than those in other liver diseases and in healthy group (82-78 RU/ml, 61-57 RU/ml vs 46-41 RU/ml). In sera of patients with positive AMA or ANA, specific for PBC, antibodies directed against bacterial antigens have been found in 80% vs. 50% in sera with AMA or ANA negative. We noticed the influence of the bacterial peptide on the specific binding antigen-antibody.

Conclusion

The molecular mimicry can be one of the possible mechanisms underlying the breakdown immune tolerance and subsequent autoimmunity disease

AUTO1-0040
INFECTION AND AUTOIMMUNITY

ASSOCIATION BETWEEN FALSE-POSITIVE TORCH (TOXOPLASMOSIS, RUBELLA, CYTOMEGALOVIRUS, HERPES VIRUS, PARVOVIRUS B19, SYPHILIS) AND ANTIPHOSPHOLIPID ANTIBODIES IN HEALTHY PREGNANT WOMEN

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Background

The relationship between false positive results for infections and autoimmune diseases is well-known, while it is not still investigated in healthy population.

Method

Our study investigated in healthy pregnant women showing false positive TORCH results: (1) presence of antiphospholipid antibodies (aPL) and (2) obstetric outcome.
Data from 23 singleton healthy pregnancies with false positive TORCH results were collected. Each woman was screened for TORCH during the pre-conception assessment and/or in pregnancy. In presence of IgM positivity, when indicated, IgG avidity was evaluated and if possible, PCR on amniotic fluid sample were performed to distinguish between primary infection or false positivity. Tests for aPL were: lupus anticoagulant (LA), anti-cardiolipin antibodies (aCL), and anti-β2glicoprotein I (anti-β2GPI). The aPL tests, if positive, were repeated after 12 weeks to confirm the results.

Results

In pregnant women with false positive TORCH, the overall prevalence of positive aPL for one or more tests was 52.2%. To clarify the correlation of false-positive TORCH results with obstetric outcome, week of delivery, neonatal birth weight and neonatal birth weight percentile were analyzed. A statistically significant lower birth weight and birth weight percentile were observed in women with false-positive TORCH associated with aPL positivity (Group A) in comparison with those in women with false-positive TORCH without aPL positivity (Group B). No statistically significant difference was found for the week of delivery between two groups.

Conclusion

It would be hopeful that future studies would verify the long-life persistence of aPL positivity and identify who will develop a classical APS or other autoimmune disorders.

AUTO1-0845
INFECTION AND AUTOIMMUNITY

DENGUE VACCINE AND AUTOIMMUNE PATHOGENESIS

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Dengue is one of the most important vector-borne viral diseases.. Infection with dengue virus (DENV) causes diseases ranging widely in severity, from self-limited dengue fever to life-threatening dengue hemorrhagic fever and dengue shock syndrome. Vascular leakage, thrombocytopenia, and hemorrhage are the major clinical manifestations associated with severe DENV infection, yet the mechanisms remain unclear. Besides the direct effects of the virus, immunopathogenesis is also involved in the development of dengue disease. Antibody-dependent enhancement increases the efficiency of virus infection and may suppress type I interferon-mediated antiviral responses. DENV-induced autoantibodies against endothelial cells, platelets, and coagulatory molecules lead to their abnormal activation or dysfunction. Molecular mimicry between DENV proteins and host proteins may explain the cross-reactivity of DENV-induced autoantibodies. The recently marketed tetravalent, live attenuated vaccine is currently indicated in most dengue-endemic countries. Trials in 10 endemic countries in Asia and Latin America showed it prevented 93% of severe disease and 80% of hospitalizations. However, there were more cases of severe disease if the first infection occurred after vaccination. Long range study in Nicaragua found that medium titer for dengue caused serious disease, high titer protected from it and low titer had no effect. Dengue may have persistent symptoms, as chronic fatigue, alopecia, myalgia and arthralgia, associated with alterations in some immunological parameters and FcγRIIa gene polymorphism. This could suggest an autoimmune-based disturbance.

AUTO1-0035
INFECTION AND AUTOIMMUNITY

CORRELATION OF INTESTINAL BACTERIAL LIPOPOLYSACCHARIDE ANTIBODIES AND BLOOD-BRAIN BARRIER ANTIBODIES IN IBD SUBJECTS

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Background

Individuals with intestinal barrier dysfunction are more prone to autoimmunity. Lipopolysaccharides (LPS) from gut bacteria have been shown to play a role in systemic inflammation leading to the opening of the blood-brain barrier (BBB), activate astrocytes and microglia and contribute to neuroautoimmunity. This study aimed to examine the effect systemic LPS has on the BBB.

Method

We tested 188 subjects with diagnosed irritable bowel disease (IBD). Subjects were assessed for serum IgG, IgA and IgM reactivities to LPS, occludin, human aquaporin, and BBB proteins. We compared the LPS positive subjects to the reactivities against intestinal tight junction, BBB and astrocytic proteins.

Results

188 subjects tested. Those over 2 standard deviations above the mean resulted as 72% were positive for LPS. In the LPS IgG positive group the IgG immune reactivity was: 48% occludin, 42% aquaporin, 34% BBB. In the IgA positive group the IgA immune reactivity was: 40% occludin, 52% aquaporin, 57% BBB. In the IgM positive group the IgM immune reactivity was: 55% occludin, 58% aquaporin, 50% BBB.

Conclusion

This study shows that systemic LPS and LPS antibodies, can significantly impact the BBB and put the nervous system at risk for neuroautoimmunity. IgG to LPS was the most common immune reactivity found, in our group of IBD subjects, followed by IgM and IgA. IgM reactivity to LPS had the highest percent of reactivity to all three self-proteins (39%). IBD patients should be screened for LPS antibodies in an effort to detect or prevent possible BBB damage, which is the gateway to neuroautoimmunity.

AUTO1-0401
INFECTION AND AUTOIMMUNITY

A SYSTEMATIC ANALYSIS OF IMMUNOGLOBULIN AND COMPLEMENT PATHWAYS IN PATIENTS WITH ACUTE RHEUMATIC FEVER

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Background

Acute rheumatic fever (ARF) is an auto-inflammatory sequela that can develop after a Group A *Streptococcus* infection. Carditis, the most severe ARF manifestation, can lead to permanent heart valve damage and rheumatic heart disease. While immunoglobulin and complement were first observed in the myocardium and mitral valves of children who had died from cardiac failure following ARF over 50 years ago (Kaplan 1964), contemporary investigations of complement pathways in ARF have been lacking. The aim of this study was to determine how complement drives inflammation in ARF.

Method

The concentration of 17 complement factors spanning the classical, lectin and alternative pathways, together with six different immunoglobulin isotypes and subclasses were measured in participant serum using bead-based immunoassays (BD Cytometric Bead Array and Luminex xMAP). An integrative statistical approach was utilised to analyze relationships among immunoglobulin and complement in ARF patients stratified by concentration of C-reactive protein (CRP).

Results

Patients with high CRP had significantly elevated levels of several complement factors and immunoglobulin types compared with low CRP patients and healthy controls. Key features contributing to ARF inflammation were identified by multidimensional analysis combining feature selection (the least absolute shrinkage and selection operator; LASSO) and principle component analysis (PCA). Just 4 of the 23 analytes accounted for 82% of the variance between high CRP patients and controls. Notably, patients in the high CRP group exhibited linked IgG3/C4 responses.

Conclusion

The linked IgG3/C4 responses, together with an absence of any lectin pathway features, suggests a dominant role for the classical complement pathway in ARF immunopathogenesis.

AUTO1-0461
INFECTION AND AUTOIMMUNITY

IS HUMAN CYTOMEGALOVIRUS A VIRAL TRIGGER OF ANTI-RO52 ANTIBODIES IN PATIENTS WITH SYSTEMIC SCLEROSIS AND SYSTEMIC LUPUS ERYTHEMATOSUS?

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Background

Early studies implicated human cytomegalovirus as trigger of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) and in the induction of anti-Ro52 in SSc but not in SLE (Zhu J Clin Exp Immunol 1996). More recent studies clearly demonstrate an association of anti-CMV with SS-A autoantibodies but whether Ro52 is involved remains unclear (Agmon-Levin N et al Clin Exp Rheumatol 2017).

Aim: To seek for antigen-specific associations of anti-CMV responses in anti-Ro52 antibody positive patients with autoimmune rheumatic diseases.

Method

Tests were performed in 59 anti-Ro52 antibody positive and anti-CMV antibody positive patients including 29 with SLE and 30 with SSc. Thirty two healthy individuals, all anti-Ro52 antibody negative but anti-CMV antibody positive, were tested as normal controls (NCs). Antigen specific antibody responses against CMV were tested by immunoblot.

Results

Antibody responses against the CMV antigens UL57, UL83, UL55, UL44, p38 and UL99 antigens were present in 29 (96.6%), 30 (100%), 20 (66.7%), 26 (86.7%), 26 (86.7%) and 27 (90%) patients with SLE, respectively compared to 29 (100%), 23 (79.3%, p=0.01), 19 (65.5%), 14 (48.3%, p=0.002), 15 (51.8%, p=0.005) and 25 (86.2%) patients with SSc, respectively.

Conclusion

While CMV is a common virus, responses against specific CMV antigens differ amongst healthy individuals and patients with autoimmune rheumatic diseases such as systemic lupus erythematosus or systemic sclerosis. In patients with anti-Ro52 antibodies, CMV reactivity against specific antigens depends on whether patients have systemic lupus erythematosus or systemic sclerosis.

AUTO1-0601
INFECTION AND AUTOIMMUNITY

"MULTIFOCAL POLYDYSBIOSIS"—APPRECIATING THE VARIOUS LOCATIONS AND CONTRIBUTIONS OF DYSBIOTIC COLONIZATIONS: ASSESSMENT AND PHARMACOLOGIC AND NONPHARMACOLOGIC TREATMENT IN AUTOIMMUNE AND INFLAMMATORY DISEASE

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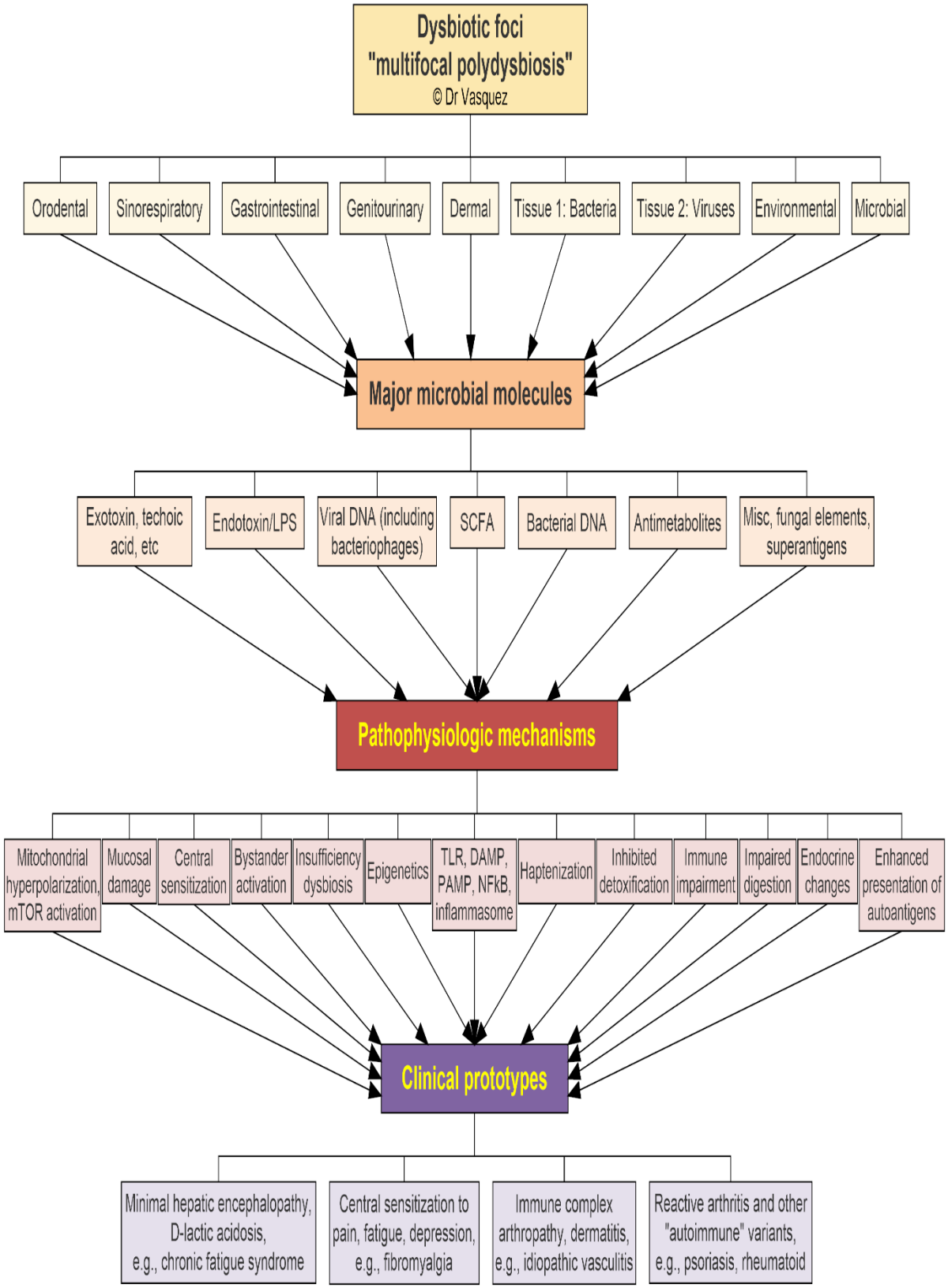
Background

Reactive arthritis (formerly Reiter's syndrome) is the widely-accepted and well-known prototype of inflammatory arthritis induced by microbial colonization, overt infection. Other, lesser-known variants of this theme include "dermatitis-arthritis syndrome" and "short bowel syndrome" which presents as variations of immune-complex and allergy-mediated vasculitis, arthritis, and dermatitis. Now, thanks to additional study and the development of more advanced laboratory techniques such as 16s-rRNA sequencing, clinicians increasingly appreciate the role of pro-inflammatory microbial colonizations and imbalances (dysbiosis) in the pathogenesis of psychiatric illness (eg, depression, autism [doi:10.1111/nyas.13516]), metabolic disease (eg, diabetes, fibromyalgia [doi:10.1038/nrrheum.2016.25]), allergy (eg, atopic dermatitis), and autoimmunity (eg, psoriasis and rheumatoid arthritis).

Method

To understand and apply this information documenting the contributory role of dysbiosis in various locations by different microbes (multifocal polydysbiosis), clinicians require an efficient review of the literature with an emphasis on practical and available assessments and interventions.



Results

The clinical research supports the model of multifocal polydysbiosis having major locations in 1) gastrointestinal tract, 2) sinorespiratory tract, 3) orodental cavity, 4)

genitourinary tract, 5) skin surface, 6) parenchyma/tissue, and 7) environment. Each of these foci can be assessed and treated with antimicrobial interventions. Importantly, enhancing overall immune defenses and immunotolerance can help to reduce colonizations, viral replication, and excessive inflammatory responses to otherwise benign microbes.

Conclusion

Clinicians and patients dealing with inflammatory and metabolic disorders will benefit from addressing the pro-inflammatory microbial component to various metabolic, allergic, autoimmune, and psychiatric disorders. The clinical data is most compelling via successful evidence-based assessments and interventions in autism, psoriasis, fibromyalgia, and atopic dermatitis.

AUTO1-0054
INFECTION AND AUTOIMMUNITY

CONTRIBUTION OF INFECTIONS TO AUTOIMMUNE REACTIVITY AGAINST D1, D2 AND NMDA RECEPTORS IN OCD/PANDAS

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Movement, behavioral, and neuropsychiatric disorders such as Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) affect millions of children worldwide. The tics and/or OCD symptomatic of PANDAS are associated with Group A beta-hemolytic streptococcal and possibly other infections. Genetics, molecular mimicry and antibodies against multiple tissue antigens all play a role in the autoimmune abnormalities detected in PANDAS. Earlier studies showed that Streptococcus IgG antibody cross-reacted with different antigens of the basal ganglia, modifying their functions and triggering movement disorder. On the other hand, IgM molecules have much greater potential than IgG for binding to neural antigens and provoking behavioral disorders. We selected 82 blood samples from patients with OCD/PANDAS, a history of streptococcal infection, and IgG/IgM positive for streptozyme and streptococcal M5 protein antibodies. 68 of the 82 had IgG elevation, 54 showed both IgG and IgM elevation, and 14 exhibited only IgM antibody elevation. Since streptococcal antigens and neuronal brain cells can cross-react, we first measured IgG and IgM antibodies against neuronal proteins in controls and in the streptococcal IgG/IgM positive groups. Due to the multifactorial nature of neuropsychiatric and movement disorders, we also measured antibodies against gluteomorphins and dynorphins. Finally, since different pathogens play a role in neuroimmune disorders, we measured IgG and IgM antibodies against infectious agents in both control and PANDAS/OCD groups. Statistical analysis using Pearson's correlation was performed to study the linear relationship between anti-streptococcal antibodies and antibodies against neuronal antigens, dietary peptides and infections. At a p value of 0.05, although the IgG correlation for streptococcal M protein, D1, D2, NMDA receptor, asialoganglioside, alpha+beta tubulin, gluteomorphin, Borrelia, HHV-6 and gluteomorphin were significant, the r values for IgG were all very weak. However, with a p value of 0.003, the IgM results were found to be very significant (r values 0.51-0.76). This significant elevation in IgM antibodies against infectious agents, dietary peptides, and brain receptors indicate that factors other than streptococcal infections are implicated in neuropsychiatric disorders. Based on our findings, it is reasonable to suggest that IgM may play a unique role in the precipitation of behavioral disturbances.

AUTO1-0664
IVIG MIMETICS: POTENTIAL NEXT GENERATION BIOLOGICS IN AUTOIMMUNE DISEASES

EFICACY AND SAFETY OF INTRAVENOUS IMMUNOGLOBULIN IN RITUXIMAB ASSOCIATED SECONDARY ANTIBODY DEFICIENCY IN RHEUMATIC DISORDERS

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Background

Rituximab administration is associated with symptomatic secondary antibody deficiency (SAD) in a small subset of patients who receive this monoclonal antibody in rheumatic diseases. Severe or recurrent infections are frequently observed in these cases. There are no established guidelines for evaluating and treating symptomatic SAD.

Method

Intravenous immunoglobulin (IVIG) replacement therapy represents the standard treatment for SAD in B-cell lymphoproliferative disorders and bone marrow transplantation. In this retrospective study we evaluated efficacy (serum IgG trough levels, incidence of re-infections) and safety (incidence of adverse events) of IVIG (400mg/kg/month) in a small serie of 10 patients with rheumatic disorders treated with Rituximab. All patients received non specific IVIG. The clinical indication was the presence of severe or recurrent infections. SAD was defined as the presence of IgG hypogammaglobulinemia (IgG < 600 mg/dL) and low specific antibody levels to pneumococcal antigens.

Results

Rheumatic disorders: SLE (2), dermatomyositis (2), vasculitis (2), polymiositis (1), optic neuromyelitis (1), undifferentiated connective tissue disease (n=1), Wegener granulomatosis (1). IVIG replacement therapy appeared to be effective in replacing IgG concentration as well as of specific antibodies (542 vs 865 mg/dL, p=0.02 and 2.98 vs 3.86 mg/dL, p=0.12) and in reducing the incidence of re-infectious events after IVIG introduction (3.8 vs 1 episodes, p<0.001). IVIG infusions were well tolerated. Low number of mild adverse events was registered, with no serious adverse events.

Conclusion

Our results suggest that IVIG is safe and effective in patients with SAD associated to Rituximab use in rheumatic disorders. These results warrant confirmation in a clinical trial.

AUTO1-1078
LATE BREAKING ABSTRACT SESSION

POSITRON EMISSION TOMOGRAPHY (PET) AND SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) IMAGING OF MACROPHAGES IN LARGE VESSEL VASCULITIS: CURRENT STATUS AND FUTURE PROSPECTS

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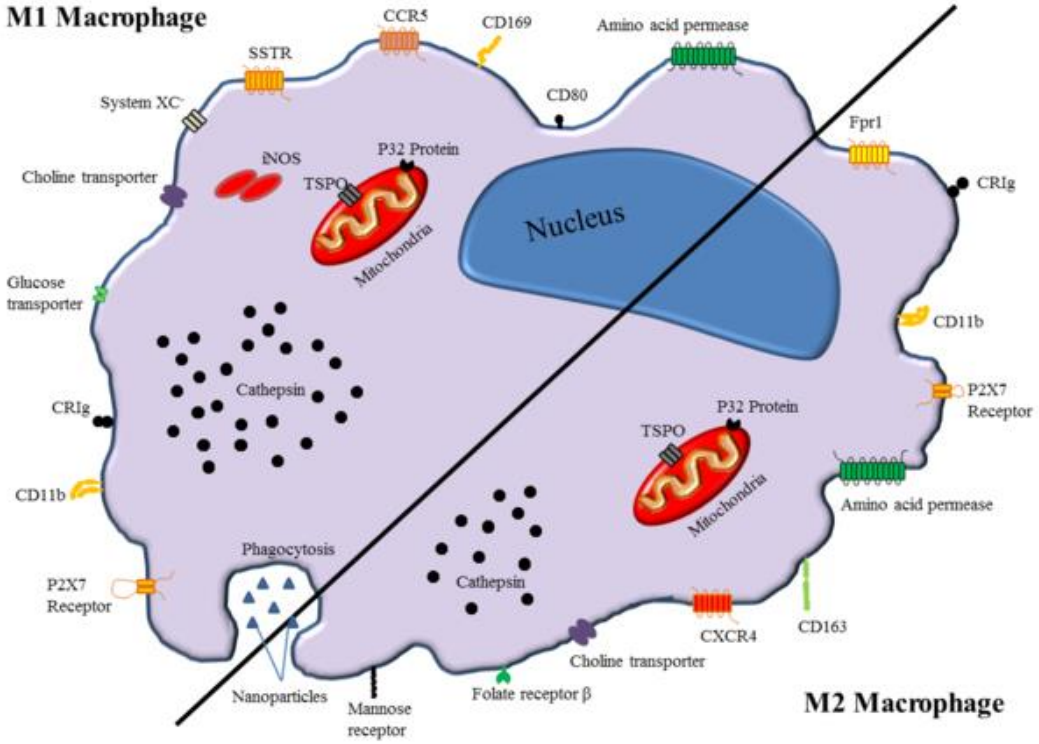
Macrophages are key players in the pathogenesis of large-vessel vasculitis (LVV) and may serve as a target for diagnostic imaging of LVV. The radiotracer, 18F-FDG has proven to be useful in the diagnosis of giant cell arteritis (GCA), a form of LVV. Although uptake of 18F-FDG is high in activated macrophages, it is not a specific radiotracer. Its uptake is high in any proliferating cell and other activated immune cells resulting in high non-specific background radioactivity especially in aging and atherosclerotic vessels which dramatically lowers the diagnostic accuracy. Evidence also exists that the sensitivity of 18F-FDG PET drops in patients upon glucocorticoid treatment [1-3]. Therefore, there is a clinical need for more specific radiotracers in imaging GCA to improve diagnostic accuracy. Numerous clinically established and novel radiotracers targeting various markers expressed on macrophages (Figure 1) developed for imaging oncological and inflammatory diseases can potentially be utilized for LVV imaging. These tracers are more target specific and therefore may provide lower background radioactivity, higher diagnostic accuracy and potentially can be used to assess treatment effectiveness. However, current knowledge regarding macrophage subsets in LVV lesions is limited. Further understanding regarding macrophage subsets in vasculitis lesion is needed for better selection of tracers and new targets for tracer development.

Figure 1. Distribution of macrophage specific radiotracer targets. These markers are generally expressed in all activated macrophages. However, some markers are highly upregulated on M1 macrophage while the others are expressed more on M2 macrophages. This figure summarized the expression of these markers based on their dominant expression on M1 and M2 subsets.



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AUTO1-0748
LATE BREAKING ABSTRACT SESSION

THE LEVELS OF MAJOR VAULT PROTEIN IN SYSTEMIC AUTOIMMUNE DISEASES

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Background

Vaults are the largest cytosolic ribonucleoprotein particles ever described. They consist of Major Vault Protein (MVP), two other proteins (TEP1, VPARP) and RNAs. TEP1 shares sequence similarity with Ro autoantigen, while vault RNA is complexed with another autoantigen the La protein. Some studies indicate the existence of autoantibodies against MVP in Systemic Lupus Erythematosus (SLE). In addition, high expression of MVP was observed in the synovial tissue lining layer of Rheumatoid Arthritis (RA) patients. Our previous study indicates that MVP is elevated in patients with RA. In this study, we sought to evaluate the levels of MVP in sera of patients with different autoimmune diseases.

Method

MVP levels were quantified in serum of 115 patients with systemic autoimmune diseases namely, SLE, primary Sjogren's Syndrome (pSS), Mixed Connective Tissue Disease (MCTD), Scleroderma (SCL) and 22 healthy individuals, using a MVP sandwich ELISA. We also measured the levels of of anti-Ro, anti-La, anti-Sm, anti-RNP, anti-Jo1, anti-SCL70, anti-dsDNA in the same patient sera using commercial ELISA assays.

Results

MVP levels were found to be similar in all patients and healthy individuals. However, elevated MVP levels were found to be correlated with the presence of anti-Scl70 and anti-Sm (χ^2=7,81, $p<0.005$) but not with the other antibodies. A weak correlation observed in the case of anti-RNP.

Conclusion

MVP levels are not remarkably elevated in patients with systemic autoimmune diseases. On the grounds that MVP levels are elevated in some autoimmune diseases (e.g. RA) and low in others, the mechanisms which provoke this phenomenon need to be investigated.

AUTO1-0639
LATE BREAKING ABSTRACT SESSION

TO ASSESS WHETHER THERE IS AN ASSOCIATION BETWEEN HYPERMOBILITY AND SPORTS INJURY

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Background

Joint Hypermobility (JH) is an extremely heritable condition in which joints have a range of motion beyond normal limits.

Anecdotal evidence suggests that being hypermobile increases the likelihood of sustaining injury whilst participating in sports due to increased joint laxity and reduced core strength.

Method

A quantitative observational approach using a cross sectional survey was adopted to collect the desired data. A variety of university sports teams were included (football, rugby, netball, hockey and running).

Individuals were identified as being hypermobile or not using the Beighton scale. All participants were then asked to complete two questionnaires; the first asking demographic information and the second questionnaire was injury specific.

Chi squared or Fisher's Exact was then used to determine if there was any significant relationship.

Results

A total of 85 students participated in the study. 20 (24%) participants were found to be hypermobile. Of the hypermobile individuals 60% (12) were female and 40% male (8) but there was no statistically significant association between sex and prevalence of hypermobility ($p = 0.196$).

There was no overall relationship between hypermobility and injury ($p = 0.804$). There was also no relationship when this was categorised into sport, netball ($p = 0.294$), running ($p=0.632$), football ($p=1.0$), rugby ($p=0.529$) and hockey ($p = 1.0$).

Conclusion

Despite literature suggesting that hypermobility may be a factor in being more likely to obtain an injury in certain sports this is not supported by this project.

This project is currently being extended to other sports including gymnastics, trampolining, track and field and ladies football.

AUTO1-0921
LATE BREAKING ABSTRACT SESSION

OXIDATIVE POSTTRANSLATIONALLY MODIFIED NEOANTIGENS AS BIOMARKER FOR AUTOIMMUNE DISEASE

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Our studies have been mostly focused on studying the mechanisms that lead to the formation of disease - and tissue-specific, neoepitopes in autoimmune diseases. We discovered that auto reactivity in autoimmune diseases is against oxidative posttranslationally modified neoantigens (oxPTM). We showed that autoantibodies to oxPTM collagen type II (oxPTM-CII) neoantigens are biomarkers that can be utilised for early diagnosis and for stratification of patients with rheumatoid arthritis. Similarly oxPTM-CII antibodies are present in spondylitis arthritis. Additional example for the involvement of oxidative posttranslational modification in autoimmune disease is type 1 diabetes (T1D). We discovered that oxPTM insulin is a neoantigen in T1D. Hence, autoantibodies to oxPTM-insulin are biomarkers for early diagnosis of T1D. More recently, we revealed that reactivity to oxPTM-insulin could predict development of T1D, even in children who were negative for gold standard serological tests. In conclusion, oxidative posttranslational modification play a role in autoimmune disease pathogenesis and can be used to identify disease tissue specific biomarkers for early diagnosis and prediction of the disease.

AUTO1-0468
LATE BREAKING ABSTRACT SESSION

REMISSION IN SLE: TESTING THE IMPACT OF DIFFERENT DEFINITIONS ON DAMAGE

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Background

To evaluate different definitions of remission and their effect on damage accrual in systemic lupus erythematosus (SLE).

Method

We considered 293 caucasian SLE patients followed-up for 7 years (2009-2015): 253 (86.3%) were female, mean±SD disease duration 11.1±7.8 years. Disease activity was assessed by clinical SLEDAI-2K (c-SLEDAI) and damage by SLICC/ACR Damage Index (SDI). We tested different definitions of remission: c-SLEDAI=0; c-SLEDAI≤1; c-SLEDAI=0 and prednisone≤5mg/day; c-SLEDAI≤1 and prednisone≤5mg/day; c-SLEDAI=0 and PGA<0.5; c-SLEDAI≤1 and PGA<0.5; c-SLEDAI=0 and prednisone≤5mg/day and PGA<0.5; c-SLEDAI≤1 and prednisone≤5mg/day and PGA<0.5. All the definitions allowed serological activity and maintenance on anti-malarial and/or immunosuppressive/biologic. The effect of different durations of remission (1, 2, 3, 4, ≥5 consecutive years) on damage was evaluated.

Results

The proportions of patients in remission according to the different definitions are shown in Table 1. When PGA was included into definition, less patients fulfilled long-term remission.

Table 1. Proportion of patients achieving different levels of remission according to the duration of remission

	Unremmited patients	1-year remission	2-year remission	3-year remission	4-year remission	≥5-year remission
Remission Type	Number (%) of patients					
c-SLEDAI=0	29 (9.9%)	31 (10.6%)	40 (13.7%)	44 (15.0%)	23 (7.8%)	126 (43.0%)
c-SLEDAI≤ 1	24 (8.2%)	29 (9.9%)	36 (12.3%)	40 (13.7%)	22 (7.5%)	142 (48.5%)
c-SLEDAI=0 and prednisone ≤5 mg/day	35 (11.9%)	27 (9.2%)	46 (15.7%)	48 (16.4%)	24 (8.2%)	113 (38.6%)
c-SLEDAI≤ 1 and prednisone ≤5 mg/day	35 (11.9%)	26 (8.9%)	44 (15.0%)	44 (15.0%)	23 (7.8%)	121 (41.3%)
c-SLEDAI=0 and PGA<0.5	75 (25.6%)	42 (14.3%)	52 (17.7%)	48 (16.4%)	21 (7.2%)	55 (18.8%)
c-SLEDAI ≤1 and PGA<0.5	73 (24.9%)	41 (14.0%)	51 (17.4 %)	48 (16.4%)	22 (7.5%)	58 (19.8%)
c-SLEDAI=0 and prednisone ≤5 mg/day and PGA<0.5	82 (28.0%)	47 (16.0%)	55 (18.8%)	47 (16.0%)	18 (6.1%)	44 (15.0%)
c-SLEDAI ≤1 and prednisone ≤5 mg/day and PGA<0.5	80 (27.3%)	48 (16.4%)	53 (18.1%)	47 (16.0%)	19 (6.5%)	46 (15.7%)

At the end of follow-up SDI was significantly higher in unremitted and 1-year remitted patients compared with 2-,3-,4- and ≥5 year remitted patients, and in 2- and 3-year remitted patients compared with 5-year remitted patients, regardless of the definition (Table 2).

Table 2. SLICC/ACR Damage Index increase during follow-up according to the duration of remission

	Unremitted patients	1-year remission	2-year remission	3-year remission	4-year remission	≥ 5-year remission
Remission Type	Mean±SD increase in SDI (% of patients with an increase in SDI) from baseline					
c-SLEDAI=0	1.69±1.44 (82.8%)	1.45±0.93 (87.1%)	0.83±0.78 (62.5%)	0.89±0.89 (59.1%)	0.65±0.83 (47.8%)	0.36±0.61 (30.2%)
c-SLEDAI ≤1	1.75±1.45 (83.3%)	1.59±0.98 (93.1%)	0.75±0.77 (58.3%)	0.88±0.91 (57.5%)	0.68±0.89 (45.5%)	0.43±0.66 (35.2%)
c-SLEDAI=0 and prednisone ≤5 mg/day	1.71±1.34 (88.6%)	1.41±0.97 (81.5%)	0.93±0.80 (67.4%)	0.75±0.75 (52.1%)	0.713±0.95 (45.8%)	0.32±0.57 (27.4%)
c-SLEDAI ≤1 and prednisone ≤5 mg/day	1.71±1.34 (88.6%)	1.42±0.99 (80.8%)	0.93±0.79 (68.2%)	0.64±0.75 (50%)	0.70±0.97 (43.5%)	0.36±0.61 (30.6%)
c-SLEDAI=0 and PGA<0.5	1.35±1.14 (78.7%)	1.05±1.01 (64.3%)	0.62±0.77 (48.1%)	0.71±0.77 (54.2%)	0.24±0.44 (23.8%)	0.18±0.43 (16.4%)
c-SLEDAI ≤1 and PGA<0.5	1.34±1.16 (78.1%)	1.05±1.02 (63.4%)	0.61±0.75 (49.0%)	0.73±0.79 (54.2%)	0.32±0.57 (27.3%)	0.21±0.45 (19.0%)
c-SLEDAI=0 and prednisone ≤5 mg/day and PGA<0.5	1.32±1.14 (76.8%)	0.94±0.96 (59.6%)	0.56±0.69 (47.3%)	0.60±0.832 (42.6%)	0.283±0.46 (27.8%)	0.23±0.48 (20.5%)
c-SLEDAI ≤1 and prednisone ≤5 mg/day and PGA<0.5	1.33±1.14 (77.5%)	0.92±0.96 (58.3%)	0.60±0.72 (49.1%)	0.57±0.83 (40.4%)	0.32±0.48 (31.6%)	0.24±0.48 (21.7%)

At multivariate analysis, a remission lasting at least 2 years was an independent predictor of no damage accrual only in the definitions including prednisone intake ≤5mg/day and/or PGA<0.5.

Conclusion

The addition of prednisone≤5mg/day and/or PGA<0.5 to c-SLEDAI=0/≤1 increases the ability to predict the absence of damage accrual.

AUTO1-0328
LATE BREAKING ABSTRACT SESSION

ASSESSMENT OF ANNEXIN A2 IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Annexin A2 (ANXA2) is a phospholipid-binding protein. Antibodies against ANXA2 have been detected in patients with Systemic Lupus Erythematosus (SLE), an auto-immune disease partly due to an impaired clearance of apoptotic material. The aim of our pilot study was to correlate ANXA2 levels with specific organ involvement and disease activity assessed by the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) and some classical biomarkers.

Method

We used a commercial ELISA sandwich kit to detect ANXA2 in the serum and urine of 43 SLE patients prospectively enrolled in our department of Internal Medicine. We also assessed serum ANXA2 levels in age and sex-matched controls.

Results

Fourteen patients had SLE-associated nephropathy, 8 had central nervous system involvement, 23 had cardiovascular involvement ; 11 also had APS (antiphospholipid syndrome). Serum median ANXA2 level was 5,7 ng/ml in patients and 3,8 ng/ml in controls. Serum ANXA2 levels did not differ in patients and controls (p = 0,166). There was no correlation between serum ANXA2 and urinary ANXA2, specific organ involvement and SLEDAI. There was a correlation between urinary ANXA2 and central nervous system involvement (p = 0,017), APS (p = 0,045), and SLEDAI (ρ = 0,32, p = 0,045). Serum and urinary ANXA2 did not correlate with the classical biomarkers of disease activity.

Conclusion

Serum ANXA2 can’t be used to assess specific organ involvement or disease activity in SLE patients. Urinary ANXA2 could be used as a biomarker of disease activity. Other studies are needed to confirm these results.

AUTO1-0854
LATE BREAKING ABSTRACT SESSION

MUSIC INFLAMMATION AND PAIN

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Introduction:
Since antiquity, within Greek mythology as also numerous biblical references, Music was considered as powerful means for relieving anxiety, depression and stress on the one hand yet potentially also effecting negatively human behavior and wellbeing.
In recent years several scientific investigations of the effect of Music on pain, as a symptom in different clinical settings including rheumatic diseases, on stress and on degenerative CNS diseases, were carried out, using various objective methods in order to assess quantitatively the efficacy of adding Music to conventional therapies in such medical situations.
Methods:
In my presentation, I will discuss these new findings via a meta-analysis of studies and randomized controlled studies originating from Music Therapy and Music Medicine disciplines, performed in the last decade using an internet data base search with appropriate key words.
Results:
Music interventions decreased pain significantly.
Music decreased emotional distress from pain
Music intervention reduced anesthetic, opioid and non-opioid usage during and after medical procedures.
Music intervention was able to reduce inflammatory cytokines parallel to the reduction of pain.

Coclusions:
Adding Music therapy to conventional treatment modalities of diseases which cause pain in general and to those with inflammatory type pain in particular, may contribute positively to patients coping with acute as well chronic medical diseases.
Additional longitudinal and controlled studies are needed for making these assumptions more conclusive.

AUTO1-0504
LATE BREAKING ABSTRACT SESSION

AUTOPHAGIC MACHINERY IN DENDRITIC CELLS PLAYS A CRITICAL ROLE IN DIABETOGENESIS BY IMPAIRING CD4 T CELL ACTIVATITION AND / OR RECRUTIMENT

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Background

Atg5 and other autophagy related proteins have been found to be necessary for optimal processing and presentation of phagocytosed antigens by conventional Dendritic Cells (DC), but the role of this process in the activation of diabetogenic CD4 and/or CD8 T-cells is unknown. Currently, we are investigating the role of the autophagy machinery (Atg5) in DC for direct priming of diabetogenic CD4 and CD8 T cells.

Method

To address this question, we crossed mice expressing CD11c- driven Cre transgenes with non-transgenic, CD4 TCR transgenic (4.1) and CD8 TCR transgenic (8.3) NOD.Atg5$^{loxP/loxP}$ mice. In these, the autophagic machinery is knocked down specifically in DC.

Results

We found that the incidence of diabetes is clearly reduced in non-transgenic (NOD ATG5 $^{loxP/loxP}$ CD11c-Cre) and 4.1-TCR transgenic (NOD 4.1 ATG5 $^{loxP/loxP}$ CD11c-Cre) mice, showing an important role for autophagy in the MHC-II driven antigen processing and/or presentation of diabetogenic autoantigens to CD4 T cells *in vivo*. On the other hand, 8.3-TCR transgenic (NOD 8.3 ATG5 $^{loxP/loxP}$ CD11c-Cre) mice only showed a minor reduction in the incidence of diabetes, showing that ATG5 deletion in DC does not impair cross-presentation of diabetogenic autoantigens to 8.3-CD8 T cells, nor 8.3-CD8 T cells recruitment and activation. No phenotypical differences have been observed in T cells from CD11c-Cre expressing 4.1 or 8.3-TCR transgenic NOD.Atg5$^{loxP/loxP}$ mice and their control counterparts.

Conclusion

Altogether, our data suggest that the autophagic machinery in DC plays a critical role in the activation of diabetogenic CD4 T cells, presumably via effects on exogenous antigen presentation of diabetogenic autoantigens.

AUTO1-0926
LATE BREAKING ABSTRACT SESSION

ANTIBODIES TO TYPE II COLLAGEN: A NOVEL TOOL FOR THE DIAGNOSIS OF SPONDYLOARTHRITIS ?

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Background

Spondyloarthritis (SpA) are an inflammatory joint disease with chronic, progressive, axial inflammation of the spine and the sacroiliac joints. Diagnosis of SpA is done criteria by clinical symptoms, radiology and MRI or ultrasound following ASAS criteria.

The aim of our study is to test whether a novel assay that we developed for RA can be used for SpA diagnosis. We have previously showed that antibodies to oxidative post-translationally modified collagen type II (oxPTM-CII) are present specifically in RA patients whether ACPA positive or negative.

Method

OxPTM-CII were generated using ribose and various reactive oxidants, and then they were analysed by SDS-PAGE. Binding to native and oxPTM-CII was evaluated by ELISA and Western Blotting. We used a cohort of sera from 67 patients with SpA, 54 patients with PsA, 49 patients with EUA. As control we used 19 patients with fibromyalgia (FM) and 70 healthy subjects. The specificity of the binding was further assessed by competitive ELISA and western blot.

Results

We detected stronger reactivity to SpA compared to PsA and even EUA serum samples. Hence specific binding to oxPTM-CII was seen in the 52% of SpA sera compared to 12% in PsA and 10% in EUA. There was no binding in samples from FM and healthy individuals. A group of the most reactive SpA samples was evaluated by western blot confirming a strong binding to several fragments or aggregates of oxPTM-CII.

Conclusion

For the first time we demonstrated that anti-ROS-CII may become a biomarker for SpA diagnosis.

AUTO1-1077
LATE BREAKING ABSTRACT SESSION

SCHIZOPHRENIA AMONG HYPOTHYROIDISM PATIENTS: CASE-CONTROL STUDY

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Background: Hypothyroidism is the most common hormone deficiency disorder resulting in insufficient thyroid hormone synthesis and release. In developed countries for whom iodine intake is adequate, Hashimoto's thyroiditis is considered to be the most prevalent thyroid disease. From early 19th century, dispersed cases linked hypothyroidism to psychosis spurring demand for higher apprehension for the contributing role of hyporthyroidism to psychiatric manifestations. Schizophrenia is considered to be of the severe psychiatric disorders, with a chronic debilitating course marked with frequent relapses

Aim: to provide insight to whether an association exists between hypothyroidism and schizophrenia

Materials and Methods: A population-based cross-sectional study was conducted using data retrieved from the largest electronic medical records database in Israel, the Clalit Health Services (CHS). Patients were defined as having hypothyroidism or schizophrenia when there was at least one such documented diagnosis in their medical records. The proportion of schizophrenia was compared between hypothyroid patients and controls. A logistic regression model was used to estimate the association between AS and COPD in a multivariate analysis adjusted for age, gender and smoking status.

Results: The study included 40,843 patients with hypothyroidism and 40,918 age- and sex-frequency matched controls. The proportion of schizophrenia in hypothyroid patients was higher than in controls (2.01% vs. 1.25%, respectively, $p<0.0001$). Multivariate logistic regression demonstrated a robust independent association between hypothyroidism and schizophrenia (OR 1.62, $p=<0.001$).

Conclusion: Our study supports an association between hypothyroidism and schizophrenia. Such interrelation provides supporting evidence to a shared etiopathologensis, and reconceptualizes the current paradigm of disease pathogeny by underscoring the plausible autoimmune basis of schizophrenia.

AUTO1-0487
LIVER AND AUTOIMMUNITY

SMALL INTESTINAL INFLAMMATION AND ALTERED MICROBIAL COMMUNITIES IN THE GUT ASSOCIATE WITH DEVELOPMENT OF AUTOIMMUNE HEPATITIS

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Background

Autoimmune hepatitis (AIH) is a disease in which loss of tolerance to self-antigens is suspected among the causes. We recently generated a mouse model, Traf6ΔTEC, with defective elimination of autoreactive T cells in the thymus which develop spontaneous AIH. The existence of the gut-liver axis that exposes the liver to bacterial antigens from the gastrointestinal tract, prompted us to examine the role of the microbiota in AIH development in our model.

Method

Mice were treated with broad range antibiotics to assess the impact of treatment on AIH. Hepatic gene expression was performed by qPCR. Microbiota analysis was performed by 16s RNAseq. Alterations in lymphocyte populations in the Payer's Patch of the small intestine were identified by flow cytometry. TLR-signaling blockage was performed by using $Trf^{-/-}$/$MyD88^{-/-}$ mice.

Results

Antibiotic treatment of Traf6ΔTEC mice resulted in reduction of AIH histopathology suggesting a role for the gut microbiota in AIH development. While the colon of Traf6ΔTEC mice was normal, these mice developed small intestinal inflammation and exhibited changes in T cell populations in the Payer's Patch (PP). This in turn associated with altered Immunoglobulin A (IgA) production and shifts in the composition of microbial communities in the gut. Blockade of bacterial recognition by Toll-like receptors (TLR) inhibited AIH histopathology.

Conclusion

Our results identify the small intestine and the gut microbiota as contributing factors to AIH development. Better understanding of how the gut and its associated microbiota regulate liver inflammation may lead to novel strategies for treating liver autoimmune inflammation and AIH pathogenesis.

AUTO1-0442
LIVER AND AUTOIMMUNITY

ROLE OF PRIMARY BILIARY CHOLANGITIS (PBC) MARKERS IN HEPATITIS C VIRUS (HCV) PATIENTS: EPIPHENOMENON?

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Background

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease characterized by immune-mediated destruction of intrahepatic bile ducts. HCV Infection is a leading cause of chronic hepatitis, cirrhosis and liver cancer. HCV Infection has been associated with induction of autoimmune phenomena/disorders. HCV diagnosis anticipates that of PBC in most patients, by many years. IFN therapy for chronic HCV infection may trigger or exacerbate an underlying autoimmune disease, including PBC. The aim of our study was to evaluate the prevalence of PBC markers in HCV patients also screened for PBC.

Method

We evaluated anti-mitochondrial antibodies (AMA), anti-sp100, anti-gp210 and ANA in 18 patients, 13 patients of whom with HCV infection, 3 patients displayed overlapping HCV-PBC, one patient overlapping HCV-AIH and the last one overlapping HCV-PBC-AIH.

Results

The HCV patients displayed a serological profile suggestive of PBC, as attested by low positivity for AMA in IIF (77%). Nevertheless, the IIF results in several cases would not be confirmed by a second level test (ELISA or DOT BLOT). The gp210, sp100 and ANA positivities were 8%, 23% and 54%, respectively. Similar immunological features in other HCV patients subtypes were observed.

Conclusion

The preliminary results of this study apparently define a «grey zone» in immunological profiles associated with PBC antigens. The increase of biochemical indices of cholestasis in HCV patients should prompt physicians to search for AMA with various sensitive techniques, as well as for PBC-specific ANA regardless of the presence of other liver diseases.

AUTO1-0583
LIVER AND AUTOIMMUNITY

ANTI-MITOCHONDRIAL ANTIBODIES AND CLINICAL VARIABILITY ASSOCIATED WITH PRIMARY BILIARY CIRRHOSIS

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Background

Anti-mitochondrial antibodies (AMA) are associated with primary biliary cirrhosis (CBP), a disease with great clinical variability.
CBP can be asymptomatic or associated with other autoimmune disease.

Method

A retrospective evaluation of the clinical course was performed in four patients with AMA positive.
Case 1- A 71-year-old female, alcoholic habits up to 50 years of age, was admitted by increased alkaline phosphatase (FA) and gamma-glutamyl transferase (GGT). She had fatigue. Drugs and hypothyroidism were excluded. ANA, SS-A, anticentromere B and A and AMA (M2, 3E) were positive. Liver biopsy showed fibrosis and inflammation.

Case 2 - A 84-year-old female was diabetic, with Raynaud's phenomenon, sclerodactyly and polyarthritis. FA and GGT were elevated. The study revealed positive ANA, anti-centromere antibodies and AMA (M2, 3E and Sp 100).

Case 3 - A 31-year-old woman with history of infectious mononucleosis, developed fatigue, polyarthritis, xerophthalmia and xerostomia. The results showed positive ANA, SS- A and ACA (M2, 3E) antibodies and rheumatoid factor. Liver biopsy revealed portal lymphocytic infiltrate and salivary glands biopsy inflammation. Sjogren Syndrome was diagnosed.

Case 4 - A 54-year-old woman, with history of hemolytic anemia was admitted with increase of FA and GGT. Echographic studies showed biliary lithiasis. ANA, AMA (M3, gp210) were detected. He was submitted to cholecystectomy and liver biopsy showed portal fibrosis and necrosis. She was asymptomatic.

Results

One patient with CBP presented only with fatigue, another was asymptomatic and Sjogren Syndrome and Scleroderma was found in the others two patients.

Conclusion

CBP has clinic and laboratory variability.

AUTO1-0490
LIVER AND AUTOIMMUNITY

NEW OPPORTUNITY FOR THE DIAGNOSIS OF PRIMARY BILIARY CHOLANGITIS (PBC): A MULTICENTER EVALUATION OF A NEW CHEMILUMINESCENCE METHOD FOR DETECTION OF ANTI-MITOCHONDRIAL ANTIBODIES

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Background

Anti-mitochondrial antibodies (AMA) are the main antibodies for PBC, usually detected by indirect immunofluorescence (IIF), despite the well-known limitations of this method. Aim of this multicenter study was to assess QUANTA Flash® M2(MIT3) on the BIO-FLASH® (Inova), in comparison to IIF rodent KSL (ANA KSL®, Inova) using a third method (Euroline Liver Disease®-LD, Euroimmun), as confirmation test.

Method

724 serum samples were tested: 153 AMA-IIF positive and 447 AMA-IIF negative, consecutively collected from the routine samples with request of AMA; 124 samples from patients with other autoimmune diseases or acute and chronic infectious hepatitis. All samples AMA positive for IIF or MIT3 were confirmed with LD.

Results

138/153 (90.1%) samples with AMA-IIF positivity were positive for MIT3 and LD (true positive); 12/153 (7.8%) were negative on MIT3 and positive on LD (false negative of MIT3); 3/153 (1.9%) were true negative of MIT3 since the positivity of AMA-IIF was not confirmed with LD (AMA different from M2).

442/447 (98.9%) samples were negative both on IIF and MIT3 (true negative); 5/447 (1.1%) were negative on AMA-IIF but positive both for MIT3 and LD (true positive).

124/124 patients with other autoimmune diseases/infectious diseases were negative both with IIF and MIT3.

Sensitivity and specificity were: 92.0% and 100% for MIT3 at the cut off proposed (20 CU) and 96.6% and 100% at the cut off calculated with ROC curve (10 CU); for IIF, using a diluition 1:40 as cut off, 96.5% and 99.4 respectively.

Conclusion

MIT3 is a very interesting alternative to IIF for detection of AMA.

AUTO1-0105
LIVER AND AUTOIMMUNITY

AUTOIMMUNE LIVER DISEASES: DOMINANCE, OVERLAP OR VARIANTS- A LARGE COHORT CLINICOPATHOLOGIC STUDY

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Background

Autoimmune hepatitis (AIH), Primary biliary cholangitis (PBC), Primary sclerosing cholangitis (PSC) are the main phenotypes of autoimmune liver diseases (AILD). Overlap designations lack well-validated diagnostic criteria; recent emphasis on variant phenotypes mandates careful correlation of histology with biochemical, serological and radiologic work-up. Liver histology considered the strongest diagnostic means, present study aimed to analyze autoimmune liver diseases for dominance, true overlaps and variants.

Method

Retrospective study of 415 of 478 patients with histological diagnosis of AILD (2010-2017), constituted the study group. Standard diagnostic criteria for AILDs and overlap syndrome with Histological activity index (HAI) score were applied. Biopsies were relooked in cases with biochemical and immunoserological overlaps or discordance.

Results

AILD (415 cases) were AIH in 250 (60.2%), PBC in 67 (16.1%), PSC in 38 (9.2%), and overlap of AIH-PBC in 60 (14.5%) cases. 20/250 (8%) of AIH showed biochemical &/or Immunoserologic overlap with PBC. 27/67 (40.3%) of PBC and 14/38 (36.8%) of PSC showed such overlap with AIH. 19/60 (31.7%) of overlap cases had laboratory favouring AIH or PBC. Relook of biopsies revealed HAI>6 in 100% (AIH, overlap) and in none (PBC, PSC). Histological diagnosis of dominant phenotype or overlap remained unaltered in 243/250 (97.2%) AIH, (100%) PSC, 64/67 (95.5%) PBC, 47/60 (78.3%) overlap syndrome.

Conclusion

AIH followed by PBC and overlap comprised majority of AILD. Biochemical & immunoserologic overlap or discordance was least in AIH and maximum in PBC. Histology along with HAI score is pivotal in recognising dominant, variant and true overlaps.

AUTO1-0542
LIVER AND AUTOIMMUNITY

WHAT ABOUT PRIMARY BILIARY CHOLANGITIS PREVALENCE IN PORTUGAL?

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Background

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease due to immune-mediated attack on the small-sized biliary ducts leading to progressive ductal destruction and loss. It is serologically characterized by the presence of anti-mitochondrial antibodies (AMA). Recently, a change of terminology, from primary biliary cirrhosis to primary biliary cholangitis, has been advocated to reflect more accurately the natural history and characteristics of this disease.

Method

We aimed at reviewing the last 10 years patients with AMA positive tests results in Centro de Medicina Laboratorial Germano de Sousa and establish prevalence rates, as well as the geographical distribution of PBC cases in Portugal.

Results

Epidemiological primary biliary cholangitis (PBC) data have generally been obtained passively and so might not indicate true rates in the general population. Incidence and prevalence rates of PBC vary widely and some researchers suggest that the incidence of PBC is growing. Differences in incidence and prevalence of PBC are probably secondary to variation in diagnostic criteria, case-finding methods, doctors' awareness, and quality of health-care systems.

Conclusion

True population-based studies are scarce and therefore large population-based studies are necessary.

AUTO1-0562
LIVER AND AUTOIMMUNITY

OVERLAP SYNDROMES IN AUTOIMMUNE LIVER DISEASE: A EIGHT-YEAR REVISED EXPERIENCE OF AN AUTOIMMUNITY CLINICAL DIAGNOSTIC LABORATORY.

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Background

Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are characterized by a varying degree of immune-mediated liver injury, and although criteria exist which facilitate their timely diagnosis, shared serological, immunological and histological patterns exist across the spectrum of these three autoimmune liver diseases. Conditions exhibiting features of two different autoimmune liver diseases are commonly designated 'overlap syndromes'.

Method

The authors present an 8-year revised casuistic as a reference clinical laboratory center in autoimmune diseases diagnosis, focusing on indirect immunofluorescent patterns, specific and associated antibodies found in PBC, AIH and PBC-autoimmune hepatitis overlap.

Results

A variant, called PBC-autoimmune hepatitis (AIH) overlap, is characterized by the above findings of PBC together with an elevated serum alanine aminotransferase, elevated serum immunoglobulin G, and circulating anti-smooth muscle antibodies (ASMA), with liver biopsy demonstrating periportal or periseptal, lymphocytic, piecemeal necrosis.

Conclusion

Primary biliary cholangitis (PBC) is an autoimmune, slowly progressive, cholestatic, liver disease characterized by a triad of chronic cholestasis, circulating anti-mitochondrial antibodies (AMA), and characteristic liver biopsy findings of non suppurative destructive cholangitis and interlobular bile duct destruction. About 10% of PBC patients, however, lack AMA.

AUTO1-0493
LIVER AND AUTOIMMUNITY

MUCOSAL AUTOIMMUNITY TO CELL-BOUND GP2 ISOFORMS 1 AND 4 IS A SENSITIVE MARKER IN SEVERE PRIMARY SCLEROSING CHOLANGITIS

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Background

Glycoprotein 2 (GP2) was demonstrated as the first autoimmune mucosal target in primary sclerosing cholangitis (PSC) associated with disease severity. Antibodies to four GP2 isoforms ($aGP2_{1-4}$) were found in patients with inflammatory bowel diseases which could be associated with PSC. Thus, the prevalence of $aGP2_{1-4}$ and their association with the clinical phenotype in PSC was investigated.

Method GP2 isoforms were stably expressed as glycosylphosphatidylinositol-anchored molecules in the membrane of HEp-2-cells and used as autoantigenic substrates in indirect immunofluorescence assay (IFA). $aGP2_{1-4}$ IgA and IgG were detected by IFA in 212 patients with PSC of four European university hospitals and 145 controls comprising 95 patients with cystic fibrosis and 50 healthy subjects.
Results Combined $aGP2_1$ and $aGP2_4$ IgA testing with a sensitivity of 66.0% and a specificity of 97.9% resulted in the best diagnostic performance (Youden index: 0.64) regarding all aGP2 and combinations thereof. Positive $aGP2_4$ IgA is significantly associated with the presence of cirrhosis and lethal outcome in PSC (p=0.0056, 0.0163, respectively). Logistic regression revealed the occurrence of $aGP2_1$ IgA (odds ratio [OR] 1.38, 95% confidence interval [CI]: 1.03-1.86) and $aGP2_4$ IgA (OR 1.52, 95%CI: 1.07-2.15) along with male gender (OR 0.51, 95%CI: 0.27-0.97) and older age (OR 1.03 95%CI: 1.01-1.05) as significant risks for the presence of cirrhosis in PSC (overall model fit, p=0.0001).
Conclusion

Combined $aGP2_1$ and $aGP2_4$ analysis is preferred to single aGP2 isoform autoantibody testing for sensitive PSC serology. Occurrence of $aGP2_{4/1}$ IgA is associated with the presence of cirrhosis in PSC.

AUTO1-0366
LUPUS: WHAT IS NEW?

IGE IN LUPUS PATHOGENESIS: FRIENDS OR FOES

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Background

Systemic lupus erythematosus (SLE) is classically considered as a Th1, Th17 and type I interferon (IFN) driven disease. Nonetheless, several studies have suggested a variable Th1 to Th2 balance that may direct disease phenotype. Lupus nephritis (LN) is illustrative of this point as proliferative forms (class III/IV) are predominantly Th1-driven, while membranous forms (class V) are rather Th2-mediated.

Method

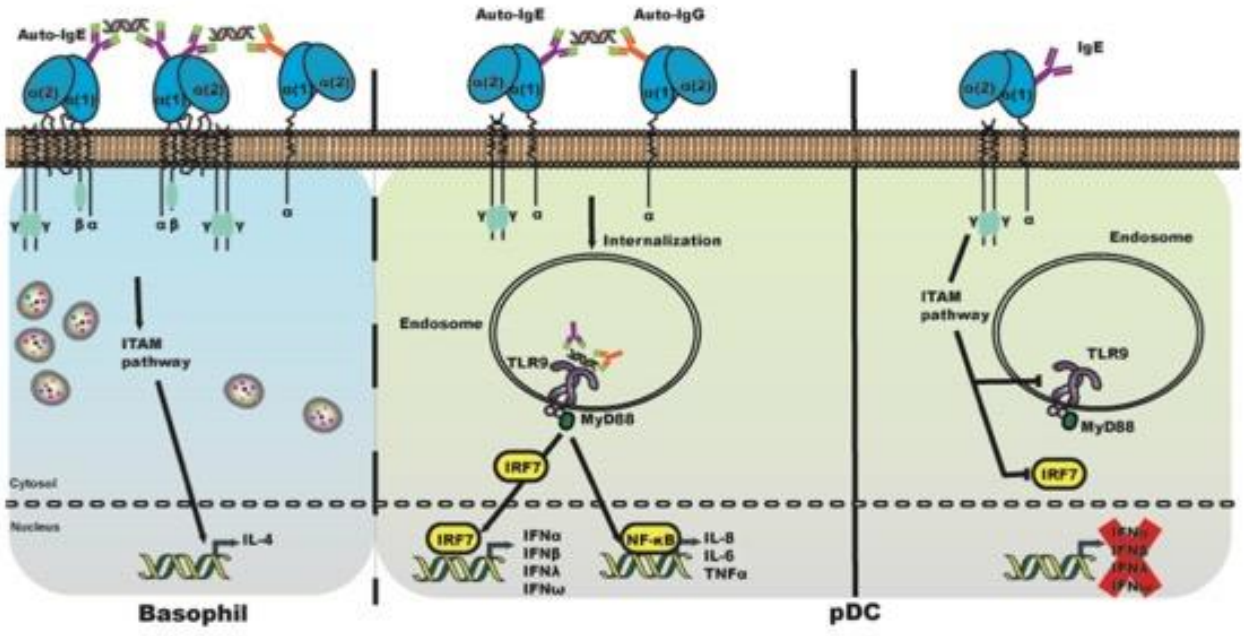
Several recent studies have highlighted the implication of the Th2 arm of immunity in the pathophysiology of SLE.

Results

Autoreactive IgE have been demonstrated to be contained in circulating immune complexes along with auto-reactive IgG and to increase the type I IFN pathways by plasmacytoid dendritic cells (pDCs). On the other hand, non-autoreactive IgE have been demonstrated to tune down the type I IFN production by engagement of the FcεR1 receptor on pDCs.

Conclusion

Finally this appears as a novel axis of SLE pathophysiology connecting IgE, basophils, plasmacytoid dendritic cells and type I IFN signature. Auto-reactive IgE are the orchestrators of this Th2 axis, while non autoreactive IgE have opposite effects, supporting the concept of an IgE paradox (**Figure**). Finally, these observations parallel the complex and not yet fully resolved IgG paradox observed in autoimmune diseases.



AUTO1-0047
LUPUS: WHAT IS NEW?

PERFORMANCE OF THE 2012 SLICC CLASSIFICATION CRITERIA VERSUS THE 1997 ACR CLASSIFICATION CRITERIA IN ADULT AND JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background

Our objective was to evaluate the performance in classifying systemic lupus erythematosus by the 2012 Systemic Lupus International Collaborating Clinics criteria (SLICC'12), versus the revised American College of Rheumatology criteria from 1997 (ACR'97) in adult and juvenile SLE patients.

Method

A systematic literature search was conducted in PubMed and Embase for studies comparing SLICC'12 and ACR'97 with clinical diagnosis. A meta-analysis was performed to estimate the sensitivity and specificity of SLICC'12 and ACR'97. To assess classification earlier in the disease by either set, sensitivity and specificity were compared for patients with disease duration <5 years. Sensitivity and specificity of individual criteria items were also assessed.

Results

In adult SLE (nine studies: 5236 patients, 1313 controls), SLICC'12 has higher sensitivity (94.6% vs. 89.6%) and similar specificity (95.5% vs. 98.1%) compared to ACR'97. For juvenile SLE (four studies: 568 patients, 339 controls), SLICC'12 demonstrates higher sensitivity (99.9% vs. 84.3%) than ACR'97, but much lower specificity (82.0% vs. 94.1%). SLICC'12 classifies juvenile SLE patients earlier in disease course. Individual items contributing to diagnostic accuracy are low complement, anti-ds DNA and acute cutaneous lupus in SLICC'12, and the immunologic and hematologic disorder in ACR'97.

Conclusion

Based on sensitivity and specificity SLICC'12 is best for adult SLE. Following the view that higher specificity, i.e. avoidance of false positives, is preferable, ACR'97 is best for juvenile SLE even if associated with lower sensitivity. Our results on the contribution of the individual items of SLICC'12 and ACR´97 may be of value in future efforts to update classification criteria.

AUTO1-0137
LUPUS: WHAT IS NEW?

FACTORS RELATED TO MORTALITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with several complications associated with mortality: cardiovascular, kidney involvement, and infections, among others. Currently it continues to be a challenge to identify the factors that can predict the probability of death [1], [2].The objective of this study is describe the factors related to death due to SLE.

Method

A description was made of a series of patients diagnosed with SLE whom died in a high complexity center in Colombia.

Results

After a follow-up of 6 years, 49 patients were included. The average age was 40.6 years (SD ± 17.4) at time of death, 44 were women (89.8%). They had a median of 4.5 years of duration of the disease. At the time of death, 89% of patients presented lymphopenia, 38% had active lupus nephritis and high SLEDAI of 19 (IQR (11-39)) (Table 1). The main cause of death was progression of SLE in 22 patients (44.9%), especially associated with catastrophic antiphospholipid syndrome (CAPS), followed by bacterial infections (n = 15, 30.6%) and cardiovascular causes (n = 5, 10.2 %) (Table 2). In a subgroup of patients with complete follow-up since diagnosis to death, a tendency to low C3 levels, increase in SLEDAI, use of cyclophosphamide and elevation of the steroid dose prior to the fatal outcome was observed (Table 3).

Table 1. Characteristics of mortality in patients with SLE.

Characteristic	N (%)*
Age	**40.6 ± 17.4**
Female gender	**44 (89.8)**
Years of duration of SLE	4.5 (2-8)
Previous hospitalizations due to lupus flares	
0	18 (36.73)
1	24 (48.98)
2 or more	7 (14.29)
Characterists at the time of dead	
SLEDAI **	*19 (11-39)*
Lupus nephritis **	*19 (38.77)*
AntiDNA positive	21 (42.8)
Creatinine (mg/dL)**	*2.3 (1.2-4.4)*
Anemia	44 (89.8)
Leukocytosis	38 (77.5)
Leukopenia	27 (55.1)
Neutropenia	21 (42.8)
Lymphopenia	44 (89.8)
Thrombocytopenia	36 (73.4)
Associated APS	15 (30.6)
Associated rheumatoid arthritis	7 (14.29)
Associated Raynaud's phenomenon	7 (14.29)
Other autoimmune disease	4 (8.1)
Bacterial infection at moment of death	**37 (75.51)**
Fungal infection at moment of death	**17 (34.6)**
Viral infection at moment of death	**13 (26.5)**

** Mean ± SD*

*** Medium (IQR)*

Table 2. Causes of death in patients with SLE.

Causes of death	N (%)*
Death associated to SLE	**22 (44.9)**
CAPS	8 (16.33)
Lupus activity	6 (12.24)
Cerebrovascular disease	3 (6.12)
Diffuse alveolar hemorrhage	2 (4.08)
Central nervous system vasculitis	2 (4.08)
Hemophagocytic syndrome	1 (2.04)
Death for other causes	**27 (55.1)**
Infection	**15 (30.6)**
Sepsis, unspecified origin	9 (18.36)
Bacterial endocarditis	2 (4.08)
Pneumonia	1 (2.04)
Mucormycosis	1 (2.04)
Disseminated histoplasmosis	1 (2.04)
Necrotizing fasciitis	1 (2.04)
Cardiovascular	**5 (10.2)**
Massive pulmonary thromboembolism	1 (2.04)
Acute aortic syndrome	2 (4.08)
Congestive heart failure	1 (2.04)
Retroperitoneal hematoma	1 (2.04)
Other causes	**4 (8.16)**
Hepatic cirrhosis	2 (4.08)
Colon cancer	1 (2.04)
Pulmonary fibrosis	1 (2.04)
Collapse of unknown origin	**3 (6.12)**

* Mean ± SD

Table 3. Subgroup of patients with SLE with full follow-up in the institution

Complete Follow up in the hospital (n=8)	Diagnosis	1 year before death	6 months before death	Death
Emergency admissions due to lupus flares **	0 (0-1)	0 (0-1.5)	0.5 (0-1.5)	**1.5 (0-3.5)**
Complement C3 (mg/dL)**	73.5 (59-75)	70 (48.15 - 77.5)	67.5 (45-76)	**53.5 (41.6-100.7)**
Complement C4 (mg/dL)**	11.5 (7.5-16)	11 (6.4-17.4)	9 (4.6-13)	**10.89 (4.5-10)**
SLEDAI**	6 (4-11)	8 (5-23)	11 (6-14.5)	**19 (12-24.5)**
Oral steroid dose (mg) **	10 (6.2-15)	12.5 (10-25)	15 (10-35)	**40 (27.5-50)**
Number of steroid pulses received **	0 (0-1.5)	0 (0-3)	0 (0-0)	**3 (0-7)**
Cyclophosphamide pulses, n (%)	0 (0)	2 (25)	2 (25)	**3 (37.5)**
Days hospitalized in general ward **	0 (0-3.5)	3 (0-11)	8 (0-27)	**12.5 (2.5-35.5)**
Days hospitalized in intensive care unit **	0 (0-0)	0 (0-2)	0 (0-0)	**11.5 (4-38.5)**

** Median (RIC)

Conclusion

Active SLE and its direct complications continue to be the main cause of death in patients with SLE, especially in young women with lupus nephritis and association with CAPS.

AUTO1-0157
LUPUS: WHAT IS NEW?

INDUCTION THERAPY OF LUPUS NEPHRITIS IN REAL LIFE SITUATION: CYCLOPHOSPHAMIDE OR MYCOPHENOLATE MOFETIL?

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Background

Low-dose intravenous cyclophosphamide (Euro-lupus) and Mycophenolate mofetil (MMF) are well established in lupus nephritis induction therapy, but few studies compared both treatments. Our aim was to compare their efficacy and safety after 6-month induction therapy.

Method

Patients with active lupus nephritis were treated with Euro-lupus (500mg, 15/15 days for 3 months) or MMF (3g/day) as induction therapy. Clinical and laboratory data were evaluated at baseline and after 6 months. Serious infectious were defined as infections requiring hospitalization and/or intravenous antibiotics. Exclusion: creatinine clearance <10mL/min and pregnancy.

Results

40 patients received Euro-lupus and 70 received MMF. Groups were comparable in age (35.23±10.32 vs. 37.43±11.43 years,p=0.316), female gender (85.0vs.84.2%,p=1.0), white race (75.0vs.62.9%,p=0.212) and disease duration (5.65±5.64 vs. 6.20±6.44 years,p=0.653). Baseline laboratory parameters, SLEDAI and glucocorticoid therapy data are shown in table 1. Frequency of previous nephritis (70.0±60.0%,p=0.312), systolic (p=0.597) and diastolic (p=0.217) blood pressure were comparable. Six-month laboratory parameters, SLEDAI and glucocorticoid therapy data are shown in table 2. After 6 months, Euro-lupus had a higher increase in C3 (p=0.038) and C4 (p=0.046) levels and a greater reduction in prednisone dose (-24.69±14.72 vs. -18.43±13.97 mg/day, p=0.029) than MMF. Euro-lupus presented higher frequency of serious infections (22.5vs.7.1%, p=0.034) than MMF.

Conclusion

Euro-lupus and MMF protocols were effective as induction therapy for active lupus nephritis with a comparable frequency of patients achieving the proteinuria target and in spite of worse baseline parameters in the former group. The higher frequency of serious infection in Euro-lupus group may be associated with more aggressive glucocorticoid regimen in these patients.

AUTO1-0042
LUPUS: WHAT IS NEW?

THE P140 PEPTIDE, A HEAT SHOCK PROTEIN INHIBITOR, MODULATES LYSOSOMAL PATHWAYS FOR LUPUS THERAPY

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Background

P140/Lupuzor™ is a phosphopeptide exhibiting significant protective properties in MRL/lpr lupus-prone mice and patients with SLE. It is currently under evaluation in phase III-clinical trials in the US and Europe.

Method

Various biochemical methods to examine the interaction between P140 and HSPA8 *in vitro* and *in vivo* were used.

Results

One of our key findings regarding the P140 mode of action is that *in vitro* P140 binds and inhibits heat shock proteins HSPA8/HSC70, a chaperone protein that plays important roles in various cellular functions. We show that it decreases HSPA8 expression on gene and protein levels, both *in vivo* in MRL/lpr mice that received the peptide intravenously, and *in vitro*, in MRL/N-1 cells, a fibroblast cell line derived from the MRL splenocytes. We discovered also that P140 significantly affects the capacity of HSPA8 to shuttle between cytosol and nucleus upon heat shock. Another important cellular function of HSPA8 is its role in chaperone-mediated autophagy (CMA), a selective autophagic pathway also mediated by chaperones HSP90AA1 and lysosomal receptor LAMP2A. By purifying lysosomes (where P140 accumulates) from the liver and spleen of MRL/lpr mice pre-treated or not with P140, and incubating these lysosomes with CMA substrates, we observed a decrease of intra-lysosome uptake of CMA substrates, confirming *in vivo* the inhibition effect of P140 on CMA.

Conclusion

The inhibition effect of P140 on HSPA8 is not only important for lupus therapy where HSPA8 has been reported to be overexpressed, but potentially also in other autoinflammatory diseases, including neurological diseases, where modulation of HSPA8 is needed.

AUTO1-0482
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

GLYCOSYLATION ALTERATIONS AS A NEW MECHANISM IN SYSTEMIC LUPUS ERYTHEMATOSUS PATHOGENESIS

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Background

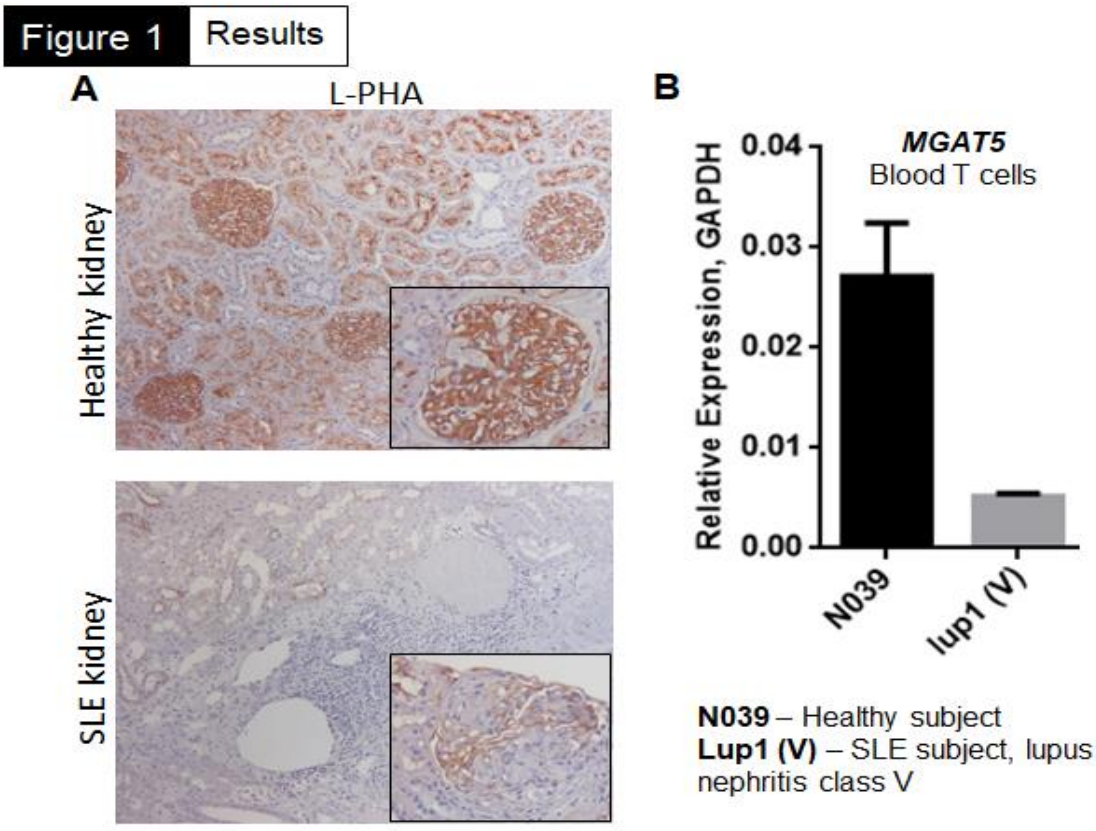
Systemic Lupus Erythematosus (SLE) is one of the most challenging autoimmune diseases for clinicians as it may be presented as a severe, relapsing and disabling immune-mediated disorder affecting multiple organs and still remaining incurable.

N-glycosylation is an essential post translational modification that participates in the correct recognition of cells by the immune system. In this study we have been addressing whether an incorrect *N*-glycosylation is associated with loss of tolerance in an autoimmune context.**Method**

Accordingly, we analysed the profile of *N*-glycosylation of a subset of biopsy-proven lupus nephritis from SLE patients and normal kidney tissue, as well as the gene expression levels of the enzyme responsible for the synthesis of these structures, MGAT5 in T lymphocytes from SLE patients' blood.

Results

We observed a significant decreased expression of a specific glycans structure in renal parenchyma, namely a decreased expression of complex branched *N*-glycans (Figure1A), when compared to healthy kidney. Complementary, the levels of gene expression of the enzyme responsible for the synthesis of these complex structures, MGAT5, was also diminished in T lymphocytes from SLE patients' blood (Figure 1B). Taken together, our observations suggest a prominent role of a branched *N*-glycans in the maintenance of self-tolerance.



Conclusion

We have demonstrated for the first time in SLE, glycosylation is a regulatory mechanism that tips the balance between homeostasis/self-tolerance and autoimmunity opening a potential novel targeted-specific mechanism in SLE pathogenesis.

AUTO1-0406
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

AUTOIMMUNITY IN AGEING: ANTINUCLEAR ANTIBODIES (ANA) AS FRAILTY MARKER IN A MULTICENTRE EUROPEAN STUDY

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Background

The increase in average life is paralleled by an enhanced number of elderly people, displaying different frailty conditions.Frailty is a clinical state associated with ageing and chronic disease, which usually anticipates disability.The FRAILOMIC initiative is a multicenter European Project designed to use biomarkers for identifying factors that may elucidate the transition from frailty into disability.The main objective is to develop clinical and laboratory tools for diagnosing and predicting the frailty risk.The antinuclear antibody (ANA) assay is used as a primary test to investigate many autoimmune disorders affecting several tissues and organs.

Method

We examined ANA in 320 elderly patients with immunofluorescence test and we tested the correlation between ANA positivity/title with the degree of frailty in the elderly.

Results

A statistically significant correlation with ANA positivity was observed in patients with frailty and disability (ADL disability $p = 0.01$; IADL disability $p = 0.05$; Mobility disability $p = 0.007$), whilst no significant association was found with other pathological conditions of the elderly, including congestive heart failure, diabetes, depression and cognitive impairment.ANA positivity, especially at low-level, seems to have a protective effect in cancer patients (22% in cancer patients vs 10% healthy patients), although this trend was not statistically significant. When we assessed all frailty conditions and divided patients into robust, pre-frailty and frailty, ANA positivity was of borderline significance ($p = 0.059$).

Conclusion

ANA testing seems an interesting screening tool for assessing the risk of frailty.The distribution of ANA positivity was different across various frailty models.

AUTO1-0115
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

THE IMPRINT OF SALIVARY SECRETION IN AUTOIMMUNE DISORDERS AND RELATED PATHOLOGICAL CONDITIONS

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Background

Xerostomia is a state of oral dryness associated with salivary gland dysfunction and is induced by stress, radiation and chemical therapy, various systemic and autoimmune diseases, and specific medications. Especially in autoimmune diseases including Sjogren's syndrome, rheumatoid arthritis, type I diabetes, systemic lupus erythematosus, progressive systemic sclerosis, and scleroderma, salivary secretion disturbance has not been successfully addressed.

Method

The proteins responsible for deficient saliva, the correlation between inflammation and salivation, autoimmune disorders and other ailments or complications associated with hyposalivation has been reviewed in the present study.

Results

Fluid secretion is interrupted by the stimulation of neurotransmitter-induced increase in cytosolic calcium ($[Ca^{2+}]_i$) in salivary gland acinar cells, prompting the mobilization of ion channels and their transporters. Salivary fluid and protein secretion are principally dependent on parasympathetic and sympathetic nerves. Various inflammatory cytokines allied with lymphocytic infiltration cause glandular damage and Sjogren's syndrome, an autoimmune exocrinopathy associated with hyposalivation. A defect in IP_3Rs, a major calcium release channel, prompts inadequate agonist-induced $[Ca^{2+}]_i$ in acinar cells and deters salivary flow. The store-operated calcium entry-mediated Ca^{2+} movement into the acini activates K^+ and Cl^- channels, which further opens a water channel protein, aquaporin-5, and triggers the release of fluid secretion from the salivary glands.

Conclusion

Xerostomia is a serious oral health problem caused by autoimmune and systemic diseases, radiation therapy, diabetes, neurological disorders, and as a side effect of certain drugs which needs to be successfully addressed under the highly developed medication treatment.

AUTO1-0184
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

NETOSIS-INHIBITING TACPA THERAPY FOR USE IN DIFFERENT NET-DRIVEN HUMAN AUTOIMMUNE DISEASES

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Background

Aberrant Neutrophil Extracellular Trap (NET) formation contributes to the induction and propagation of inflammation and plays a key role in causing tissue damage in conditions like sepsis, SLE, RA and vasculitis. In these diseases, NET components are observed in blood and inflamed tissues. Here, we demonstrate the utility of therapeutic ACPA (tACPA) as a NETosis-inhibiting therapy for NET-based diseases including SLE, RA and idiopathic pulmonary fibrosis (IPF).

Method

Neutrophils from RA and SLE donors, together with biological NET-inducing stimuli, such as RA synovial fluid (SF), gout SF and activated platelets, have been used to demonstrate the NETosis-inhibiting properties of tACPA in different human disease contexts. *In vivo*, we have tested tACPA's therapeutic utility in murine models for RA and IPF, and a surrogate model for NET-mediated organ damage (sepsis).

Results

In human SLE, RA and healthy neutrophils, NETosis induction with calcium ionophore, physiological stimuli, like gout SF or activated platelets, is strongly inhibited by tACPA treatment (40-100% reduction). These observations have been confirmed with multiple NET readouts, such as MPO activity, MPO/DNA ELISA, DNA quantification as well as imaging. In an LPS-induced sepsis model, 30% of tACPA-treated mice survived, showing protection against organ failure. In CAIA and IPF murine models, tACPA protected mice from the development of joint damage and lung fibrosis, respectively, showing a strong effect on reducing infiltrating neutrophils.

Conclusion

Our data provide strong evidence that tACPA could be a promising therapeutic strategy for diseases in which NETs are the source of auto-antigens and contribute to endothelial toxicity and organ damage.

AUTO1-0021
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

EXPANSIONS OF ATHEROGENIC, CYTOTOXIC CD28NULLCD4+ T-CELLS ARE LINKED TO RHEUMATOID ARTHRITIS-ASSOCIATED CLASS-II MHC ALLELES AND DRIVEN BY CYTOMEGALOVIRUS INFECTION BUT ONLY MARGINALLY AFFECTED BY AGE

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Background

$CD28^{null}$ CD4+ T-cells are cytotoxic T helper cells lacking expression of the co-stimulatory marker, CD28. This subset has been implicated in cardiovascular disease, autoimmune disease and in particular the combination of both. Importantly, $CD28^{null}$ CD4+ T-cells seem to destabilize plaques and promote acute events in coronary artery disease. Some reports have associated expansions of these cells with Cytomegalovirus (CMV) infection but stopped short of showing the full impact of CMV on $CD28^{null}$ CD4+ T-cell expansions.

Method

We analyzed $CD28^{null}$ CD4+ T-cell frequencies by multi-color flow-cytometry in 242 generally healthy individuals of whom 106 were CMV− and 136 CMV+. We also used ex-vivo stimulation with CMV peptides followed by intracellular cytokine staining to analyze the antigen-specificity of and additional phenotype markers on these cells. In addition, 64 individuals were HLA-typed.

Results

In CMV+ individuals the median frequency of $CD28^{null}$ CD4+ T-cells was >12-fold higher than in CMV− individuals. Interestingly, CMV-specific CD4 T-cells were significantly enriched in the $CD28^{null}$ subset and also expressed markers of vascular adhesion. Also, the presence of certain class-II MHC-alleles was significantly associated with larger/smaller frequencies of $CD28^{null}$ CD4+ T-cells among CMV+ individuals.

Conclusion

Expansions of $CD28^{null}$ CD4+ T-cells are clearly limited to CMV-infected individuals and a significant proportion of these cells recognize CMV-antigens. In future, clinicians might consider the size of this subset and the CMV infection status of patients with cardiovascular, in particular coronary artery disease, and some autoimmune conditions. Therapies targeting CMV in order to reduce the frequencies of $CD28^{null}$ CD4+ T-cells may become a realistic therapeutic option.

AUTO1-0081
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

NEUTROPHIL EXTRACELLULAR TRAPS (NETS) IN AUTOIMMUNE DISEASES

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Background

The structures named neutrophil extracellular traps (NETs) are fibrous networks which protrude from the membrane of activated neutrophils. NETs are found in a variety of conditions, such as infection, malignancy, atherosclerosis, and autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), psoriasis, and gout

Method

We performed a systematic review using the MEDLINE database to highlight the importance of NETs in the etiopathogenesis of autoimmune disease.

Results

The impact of NETs on the development mechanisms of autoimmune diseases are proposed to arise from an imbalance between “NETosis” which is a process of NET formation and NET degradation. Neutrophils, interleukin-8, ANCA and other many inflammatory molecules are considered to play a key role in NET formation. In this way, prolonged exposure to these abnormal cascade of NETs affect autoimmunity and increase the chance of systemic organ damage.

Conclusion

We discuss the specific roles of various inflammatory molecules in relationship to NETs. We will also provide evidence of the importance of NETs in the pathogenesis of autoimmune diseases and furthermore highlight the potential that target therapies may influence NET formation and associated molecules.

AUTO1-0323
MECHANISM AND PATHOGENESIS OF AUTOIMMUNITY

BLOCKADE OF CRITICAL IMMUNE REGULATORS RESULTS IN DIFFERENT ROADS TO PATHOGENESIS IN PRIMARY SJOGREN'S SYNDROME

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Background

CD40/CD40L interactions play a critical role in both immunity and autoimmunity. In this study we sought to understand the requirement for CD40 signaling in two distinct immune checkpoint pathways, PD-1 and CD28, important for maintenance of peripheral tolerance. Blocking either pathway can result in loss of self-tolerance and development of autoimmunity.

Method

Blocking of CD40/CD40L interaction.

Results

We found that primary Sjögren's syndrome (pSS) and autoimmune thyroid diseases (ATD) that develop spontaneously in CD28-deficient IFNg$^{-/-}$NOD.H-2h4 (CD28$^{-/-}$) mice required CD40 signaling. Specifically, blockade of CD40L with the anti-CD40L mAb, MR1, inhibited inflammation of thyroid and salivary gland target tissues and blocked production of disease-associated autoantibodies. Unexpectedly, however, ATD and pSS in PD-1-deficientIFNg$^{-/-}$NOD.H-2h4 (PD-1$^{-/-}$) mice developed independently of CD40-CD40L interactions. Here, treatment with anti-CD40L either had no effect or even exacerbated disease in pSS and ATD, respectively. Most interesting, anti-thyroglobulin and pSS-associated autoantibodies were increased following anti-CD40L treatment in PD-1$^{-/-}$ mice, even though MR1 inhibited spontaneous splenic germinal centers that develop in these mice. Importantly, administration of anti-PD-1 mAb to CD28$^{-/-}$ mice recapitulated the PD-1$^{-/-}$ phenotype, significantly impacting the ability of MR1 to suppress ATD and pSS in CD28-/- mice following blockade of the PD1 pathway. Finally, we found that loss of PD1 impacted type I IFN production, suggesting a CD40-independent mechanism responsible for worsening of disease.

Conclusion

These results indicate that there can be different pathways and requirements driving autoimmune pathogenesis that are dependent on the availability of specific checkpoint receptors, and an intact PD-1 pathway is important for inhibition of autoimmunity by anti-CD40L.

AUTO1-0560
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

TWEAK-BINDING ANTIBODIES (TWAB) ARE PRODUCED DURING MULTIPLE SCLEROSIS

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Background

TWEAK (TNF weak inducer of apoptosis) is a cytokine member of the TNF ligand superfamily that plays multiple roles according to the target cell type and the micro-environmental conditions. It can be involved in cell proliferation, migration, differentiation or apoptosis. We have been the first to describe a pro inflammatory role of TWEAK in multiple sclerosis (MS). Recently we have shown that TWEAK-binding antibodies (TWAb) were generated during chronic inflammatory disease (psoriatic arthritis) and could have a protective role against chronic inflammation. The prevalence of TWAb during MS is still unknown.

Method

Serum samples of 60 MS patients and 134 healthy blood donors (HBD) were collected and analyzed. For 30 out of the 60 MS patients we have obtained a second blood sample one year after the beginning of the disease. Circulating IgG TWAb were detected by a homemade-western blot assay using human recombinant TWEAK.

Results

TWAb were detected in 29/60 (48.3%) MS patients and in only 8/134 (5.9%) HBD ($p<0.05$). Moreover these antibodies were persistent. In fact all the patients who were tested twice and who were TWab positive for the first test were positive for the second test.

Conclusion

We described here for the first time the production of persistent TWab during MS. These antibodies could represent a tool for defining subgroups of MS patients. Further studies are needed to define their place in MS management.

AUTO1-0290
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

ALPHA-SYNUCLEIN AND PARKIN DYSFUNCTION BEYOND PARKINSON'S DISEASE: EXPLORING DOPAMINE SYSTEM IN THE EXPERIMENTAL MODEL OF MULTIPLE SCLEROSIS

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Background

Multiple sclerosis (MS) is the most autoimmune neurodegenerative demyelinating disease of the central nervous system (CNS) that cause neurological disability in young adults and still remains without an effective therapy. Some studies suggest molecular similarities between MS and other neurodegenerative diseases, like oxidative damage and neuroinflammation, for instance, these can be observed in Parkinson's disease.

Method

Herein, we evaluated the expression of α-synuclein (α-syn) and Parkin in the spinal cord and striatum during the EAE progression, as well as provide further evidence on the underlying pathways related to the immunomodulatory and neuroprotective effects of dopaminergic agonist during the EAE model.

Results

Our study demonstrated that EAE produced a significant increase in Parkin expression in the spinal cord and striatum, which could indicates that autoimmune neuroinflammatory processes are able to alter Parkin expression. Furthermore, up-regulation of Parkin levels can be interpreted as an attempt to remove mutated, aggregated, and misfolded proteins, such as α-syn. Moreover, a marked decrease in α-syn expression was evident in the spinal cord and striatum of EAE mice. Interestingly, α-syn and Parkin expression in the spinal cord and striatum was restored by pramipexole – a nonergot D3/D2 dopamine agonist – indicating that, during the MS progression, dopaminergic agonists can inhibit changes in the expression of proteins related to Parkinson's disease.

Conclusion

On these bases, we propose that dopamine D2/D3 receptor agonists could be used as a possible new venue for an effective MS treatment.

AUTO1-0241
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

TREATMENT WITH TWO HUMAN CHORIONIC GONADOTROPIN PREPARATIONS DIFFERENTIALLY ALTERS DISEASE ACTIVITY IN A MOUSE MODEL FOR MULTIPLE SCLEROSIS

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Background

Multiple Sclerosis (MS) is one of the most common neuroinflammatory diseases affecting young adults. Based on observations that MS patients recover during pregnancy, an involvement of pregnancy hormones in disease amelioration was suggested. Therefore, we investigated the influence of the pregnancy hormone human chorionic gonadotropin (hCG), known to possess a variety of immunomodulatory functions, on disease activity in the experimental autoimmune encephalomyelitis (EAE) mouse model.

Method

Female C57BL/6 mice were immunized using the myelin oligodendrocyte peptide (MOG_{35-59}) following a standardized protocol using complete Freud's adjuvant supplemented with *M. tuberculosis* and pertussis toxin injections. Furthermore, each mouse received an injection of either urine-derived hCG (uhCG) or recombinant hCG (rhCG) every other day, starting at the day of EAE induction. Disease progression was followed up for 35 days and samples of the central nervous system (CNS), spleen and inguinal lymph nodes were collected and evaluated by flow cytometry analysis for immunological parameters at day 35.

Results

Treatment with uhCG resulted in less pronounced disease symptoms after disease onset reaching a significant difference at day 20 compared to control mice, while rhCG did not alter disease progression. The positive effect of uhCG was associated with a decrease in the pro-inflammatory $CD4^+IL17^+$ (TH17) cell population and a significant reduction in the $CD19^+IL17^+$ (B17) population within the CNS.

Conclusion

Our results suggest that uhCG may reduce disease symptoms through modulation of TH17 and B17 cell populations. Moreover, we claim that B17 cells are involved in EAE disease progression and may represent a new potential target for therapeutic interventions.

AUTO1-0643
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

THROMBIN CLEAVAGE AND EXTRACELLULAR PROTEASOME DEGRADATION OF OSTEOPONTIN REGULATE ITS ACTIVITIES IN MULTIPLE SCLEROSIS

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Background

Osteopontin (OPN) is a proinflammatory cytokine and plays a pathogenetic role in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), by recruiting autoreactive T cells into the central nervous system. In EAE, administration of OPN during the remission induces a prompt relapse. OPN is cleaved by thrombin in two halves, the N-terminal and the C-terminal fragment.

Method

We investigated their effect in human cells in vitro and in EAE in vivo.

Results

In vitro, OPN-N increases production of IL-17 in T-cells, secretion of IL-6 in monocytes and lymphocytes migration, whereas OPN-C increases lymphocyte adhesion to vascular endothelial cells (HUVECs) and inhibits production of IL-10 in T-cells. In vivo, OPN-FL and OPN-C induce a similar strong relapse of EAE, whereas OPN-N induces a mild relapse. Moreover, we found that OPN is processed also by the extracellular 20S proteasome modulating the OPN chemotactic activity. In particular, proteasome-mediated digestion inhibits the chemotactic activity of OPN-N, whereas it elicits chemotactic activity from OPN-C. By mass spectrometry, we identified four peptides derived from proteasome-mediated digestion of OPN – $OPN_{217-230}$, $OPN_{249-266}$, $OPN_{267-278}$ and $OPN_{292-306}$- exerting a strong chemotactic activity. Conversely, OPN modulates the proteasome activity since it inhibits the proteasome release from cells in vitro. Moreover, in patients with MS, the serum levels of OPN and proteasome reflects the remission/relapse alternation.

Conclusion

These findings suggest that drugs targeting OPN fragments may be used to fine-tune the pathological effects of OPN in MS and other autoimmune diseases.

AUTO1-0212
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

IMMUNOLOGICAL EFFECTS OF DIMETHYL FUMARATE IN MULTIPLE SCLEROSIS PATIENTS

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Background

Dimethyl fumarate (DMF) is an oral drug for the treatment of relapsing-remitting multiple sclerosis (RRMS), with an anti-inflammatory effect. It is relatively well tolerated, but it has an important impact over several leukocyte subpopulations. Consequently, immune monitorization becomes necessary to understand the effect of DMF on the immune system and to relate these changes to the clinical outcome and potential adverse effects. The objective of this study is to analyze the immunological changes induced by DMF in samples of whole blood of RRMS patients.

Method

Longitudinal prospective study of peripheral blood T, B, NK, monocyte and DC subpopulations using multiparametric flow cytometry in whole blood from 12 RRMS patients under DMF treatment at baseline and after 1, 3, 6 and 12 months of follow-up.

Results

The study evidenced a selective reduction of T effector, T central and B memory cells in a 52.3±14.1%, 37.3±16.1% and 54.3±20.3%, respectively, was evidenced after 12 months. In contrast, the relative prevalence of both T and B naïve subpopulations increased in a 58.4±25.6% and 47.1±31.6%, respectively. Additionally, a switch in the central memory Th2/Th1 ratio from 0.8±0.3 to 1.4±0.6 and an increase of transitional B cells in absolute number (from 5±3 to 10±5 cells/µL) were spotted. All these changes were progressive from month 1, and already significant by month 6. All results were statistically significant ($p<0.05$).

Conclusion

The beneficial effect of DMF reducing the number of clinical relapses in MS patients seems to be related with the effect of DMF depleting effector T cells and increasing transitional B cells.

AUTO1-0257
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

DIMETHYL FUMARATE INDUCES A PERSISTENT CHANGE OF THE INNATE AND ADAPTIVE IMMUNE SYSTEM OF RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS

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Background

Dimethyl fumarate (DMF) is an oral treatment for multiple sclerosis (MS) of which the effects on the immune system are not completely elucidated. This study aimed to perform an extensive immunophenotypic analysis of the innate and adaptive immune system of DMF-treated MS patients.

Method

In a follow-up study, immune cell subtype frequencies were determined by flow cytometry in the peripheral blood of 12 MS patients before and after 12 months of DMF treatment. Similar analyses were performed in a cross-sectional study of 25 untreated and 64 DMF-treated MS patients. Direct effects of DMF on B cells were analysed *in vitro*.

Results

After 12 months of DMF treatment, frequencies of innate immune cells, including monocytes and natural killer cells, increased. In the adaptive immune system, DMF treatment decreased the frequencies of (effector) memory T cells, (non) class-switched memory B cells and double negative B cells and increased the frequencies of naive T and B cells and transitional B cells. Furthermore, frequencies of interferon-γ, granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-17 expressing $CD4^+$ T cells decreased. In the cross-sectional study, DMF was fully effective after 6 months of treatment. DMF induced direct and concentration dependent apoptosis of B cells and decreased B cell expression of the costimulatory molecule CD40, antigen presentation MHCII molecule and the survival marker B cell activating factor receptor (BAFFR).

Conclusion

In conclusion, DMF treatment induced a persistent change of the immune system of MS patients and directly induced B cell apoptosis and reduced B cell expression of functional markers.

AUTO1-0011
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

EVALUATION OF METABOLIC PROFILE IN PATIENTS WITH MULTIPLE SCLEROSIS: ASSOCIATION WITH CLINICAL AND HEMATOLOGICAL PARAMETERS

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Background

Multiple sclerosis (MS) is a complex inflammatory, demyelinating and neurodegenerative disease with a heterogeneous pathology and clinical outcomes. Vascular comorbidities, including diabetes, and hyperlipidemia, may adversely affect outcomes in MS. **Objective**: To assess the associations of serum lipid profile with clinical parameters in MS

Method

50 MS patients classified according to the 2010 McDonald criteria and 50 control subjects (CS), adjusted by age and sex, were included in this study. Serum levels of glucose (Glu), triglycerides (Tg), high and low density lipoproteins (HDL, LDL) and total cholesterol (TC) were determined by spectrophotometer methods. Very low density lipoproteins (VLDL) levels were calculated by Friedwald equation. The data was analyzed with STATA v12 software and $p<0.05$ was reported as statistically significant

Results

Levels of Glu ($p=0.003$) and TC ($p<0.001$), were more elevated; and Tg ($p<0.001$), HDL ($p=0.006$) and VLDL ($p<0.001$) were more diminuend in MS patients than CS group. Moreover, we found that Glu positively correlates with disease duration ($p=0.031$), EDDS ($p=0.001$), RDRS-2 ($p<0.001$) and FIS ($p<0.001$); TC positively correlates with disease duration ($p<0.001$), EDDS ($p=0.002$), RDRS-2 ($p<0.001$) and FIS ($p<0.001$); LDL positively correlates with disease duration ($p<0.001$), EDDS ($p<0.001$), RDRS-2 ($p<0.001$) and FIS ($p<0.001$); and HDL negatively correlates with EDDS ($p=0.005$), RDRS-2 ($p=0.004$) and FIS ($p=0.011$)

Conclusion

This study revealed that MS patients altered levels of metabolic profile regarding CS group and these levels correlated with clinical parameters. Our findings indicating the need for future research in the field, to avoiding these preventable comorbidities in MS patients.

AUTO1-0474
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

REPLICATION AND VALIDATION OF THE AUTOANTIGEN ANOCTAMIN 2 ASSOCIATION WITH INCREASED RISK FOR MULTIPLE SCLEROSIS

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Background

Multiple sclerosis (MS) is a chronic demyelinating and inflammatory disease of the central nervous system which is likely driven by autoimmune mechanisms and caused by a combination of genetic predispositions and environmental factors. We have previously identified the calcium activated chloride-channel protein Anoctamin 2 (ANO2) as an autoantigen associated to MS (Ayoglu 2013, 2016)

Ayoglu et al 2013. Autoantibody profiling in multiple sclerosis using arrays of human protein fragments. Mol Cell Proteomics.
Ayoglu et al 2016. Anoctamin 2 identified as an autoimmune target in multiple sclerosis. Proc Natl Acad Sci USA.

Method

Here we have in a replication and validation study determined IgG reactivity towards ANO2 using a multiplex suspension bead array immunoassay in a large cohort of 8700 MS cases and 7200 population-based controls from Sweden.

Results

We confirmed the finding that MS patients have significantly higher levels of anti-ANO2 antibodies compared to controls ($p=10^{-16}$) in an independent part of the dataset (7600 MS cases and 6200 controls) where individuals in our previous study were excluded. The fraction of ANO2-seropositivity was here defined as 5.2% in MS cases and 1.9% in controls resulting in an odds ratio for MS of 2.2.

The odds ratio for MS in individuals carrying the three MS risk factors: ANO2-seropositivity, *HLA-DRB1*15:01* and high antibody reactivity against EBNA1 was 16. This was twice as high compared to the odds ratio for MS in individuals with the first two factors but without ANO2-seropositivity.

Conclusion

The association of Anoctamin 2 to increased risk for multiple sclerosis is replicated and validated.

AUTO1-0432
MULTIPLE SCLEROSIS (MS); WHAT IS NEW?

DIMETHYL FUMARATE THERAPY IS ASSOCIATED WITH REDUCED MIGRATORY CAPACITY AND DECREASED PRO-INFLAMMATORY PROFILES IN B AND T CELLS IN PATIENTS WITH MULTIPLE SLCEROSIS

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Background

Dimethyl fumarate (DMF) is an oral drug for patients with relapsing remitting Multiple Sclerosis (RRMS), which we and others have shown reduces CD8 T and B cells in the periphery. The aim of this study was to assess the effect of DMF therapy on the cytokine profile and migratory capacity of immune cells in RRMS patients.

Method

Blood was obtained from 36 patients prior to and 3.5 month after DMF therapy initiation. B and T cells were cultured for 40 hours in single culture or co-culture and their cytokine profile assessed by flow cytometry. The migratory capacity of the major immune cells towards CXCL12 and CXCL13 was assessed using a transwell assay.

Results

DMF therapy was associated with a significant increase in $IL10^+$, $TGFb^+$, $IL4^+$ and $IFNg^+$, while reduction in LTa^+ and $TNFa^+$ B cells; and an increase in TGFb expression, while reduction in $TNFa^+$ and $IFNg^+$ T cells. B cells induced $TGFb^+$, LTa^+ and $IL4^+$ T cells in the co-culture, with no difference before and after therapy. The CXCL12-migratory capacity of $CXCR4^+$ immune cells, CD8 T cells and B cells (trend) was reduced after therapy, although CXCR4 expression was elevated; and while CXCL13-migration was unaffected, CXCR5 expression was reduced in B cells and monocytes. The reduction in % B cells, and % $TNFa^+IFNg^+$ T cells correlated with a reduction in disability score (EDSS) of the patients.

Conclusion

DMF therapy is associated with a shift from pro- to anti-inflammatory cytokines in B and T cells, and with reduced lymphocyte migration.

AUTO1-0797
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

MICROSTRUCTURE CHANGES IN WHITE MATTER IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: ASSOCIATION WITH DISEASE ACTIVITY AND NEUROPSYCHIATRIC MANIFESTATIONS.

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Objective: To determine the microstructural changes of the corpus callosum in patients with systemic lupus erythematosus using a semiautomatic method by diffusion tensor image (DTI) in MRI exam and also to determine the possible correlation with the neuropsychiatric, clinical manifestations and laboratory tests and treatment.
Methods: We included 116 patients with SLE (110 women, mean age 40 years) and 48 healthy controls (40 women, mean age 35.5 years). Neuropsychiatric manifestations were analyzed based on the diagnostic criteria of ACR for neuropsychiatric impairment and disease activity by SLEDAI (Systemic Lupus Erythematosus Disease Activity Index). All patients and controls underwent magnetic resonance imaging using diffusion tensor technique and fractional anisotropy (FA), mean diffusivity (MD) by Freesurfer.
Results: FA values were significantly lower in SLE compared to controls ($p < 0.001$). The group with active neuropsychiatric manifestations (NPSLE) presented significantly lower FA values ($p < 0.001$) and higher MD values ($p < 0.001$) than the SLE groups without neuropsychiatric manifestations ($p < 0.001$), with inactive NPSLE ($p < 0.001$) and controls ($p < 0.001$). Among neuropsychiatric manifestations, mood alteration ($p = 0.012$), seizure ($p = 0.001$), and cerebrovascular disease ($p = 0.034$) were associated with a reduction in FA and seizure ($p = 0.004$) with increased MD values. SLEDAI presented a positive correlation with MD ($p = 0.010$) and negative correlation with FA values ($p < 0.001$).
Conclusion: The DTI MR study may provide elements for a more comprehensive analysis of the microstructure of the white matter in patients with NPSLE.

AUTO1-0415
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

ANALYSIS OF MICRO-RNA EXPRESSION IN THE THYMUS OF MYASTHENIA GRAVIS PATIENTS OPEN NEW RESEARCH AVENUES

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Background

In Myasthenia Gravis (MG) with anti-acetylcholine antibodies, B-cell infiltrations and ectopic germinal center development are frequently observed in the early-onset form. miRNAs are non-coding RNAs acting on mRNA as post-transcriptional regulators and can be involved in pathophysiological processes. In this study, we investigated the implication of miRNAs in thymic abnormalities associated with early-onset MG.

Method

We performed a miRnome study using miRNA arrays from Affymetrix.

Results

We found 61 specific dysregulated miRNAs (24 up- and 37 down-regulated) with a fold change of 1.5 (p-value < 0.05). We also demonstrated the implication of miRNA clusters. Of particular interest, we found that a common regulatory mechanism could conjointly down-regulate the expression of FMR1 and miRNAs clustered at the extremity of the X chromosome. Their implication in MG need to be further investigated.

Among the dysregulated miRNAs, we focused our attention on the most down-regulated miRNAs: miR-7-5p. We confirmed by RT-PCR its down-regulation in MG thymuses, in particular, in thymic epithelial cells. In MG thymuses, we observed an inverse correlation between the expression of miR-7 and CCL21; a target mRNA for miR-7 according to predictive algorithms. Transfecting thymic epithelial cells with miR-7, we demonstrated a direct down-regulation of this chemokine. As CCL21 is involved in the abnormal recruitment of B cells in the MG thymus, our results suggest that miR-7 could be involved in thymic changes associated with MG.**Conclusion**

Altogether, this thymic miRnome analysis demonstrates that dysregulation of specific thymic miRNAs can be associated with MG and provides novel insights into the pathogenesis of MG.

AUTO1-0395
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

IMPLICATION OF INTERLEUKIN 23 IN THE INFLAMMATORY EVENT OCCURING IN MYASTHENIA GRAVIS THYMUS.

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Background

Myasthenia gravis is an autoimmune disease characterized by an inflammatory process in the thymus in which an overexpression of IL17 related genes and dysfunctionalities in Treg and Th17 cells have been reported (Gradolatto et al., 2014). Furthermore, differentiation of T-cells towards a pathogenic Th17 phenotype is regulated by a group of cytokines such as Interleukin 6, 21, 23 (IL-6, IL-21, IL-23) and TGF-β3 (Lee et al., 2012).

Method

Here, we investigate the level of expression of the cytokines involved in Th17 differentiation in AChR+ MG thymuses.

Results

We found that IL-6, IL-21, IL-23 and TGF-β3 are significantly overexpressed. Nevertheless, only IL-23 remain overexpressed in periphery. Additionally, we observed that MG thymic epithelial cells (TEC) overexpress IL-23. Consequently we analyze the factors that can induce IL-23 overexpression in normal TEC cultures. We found that Poly(I:C) induce the expression of IL-23 through IFN type 1(overexpressed in MG thymuses). While interferon type 2 or LPS had no effect. More, expression of IL-23 in TEC is also stimulated by IL-17.

Conclusion

Our results show that overexpression of IL-17 in MG thymuses is probably due to the overexpression of the cytokines that favor the pathogenic Th17 phenotype, especially by IL-23. We also showed that deregulation of IL-23 expression by TEC is induce by IFN type 1 and IL-17. Hence, in $AChR^{+}$ MG thymuses, differentiation of Th17 cells is maintained by a pro-inflammatory microenvironment lead by IL-23.This creates an inflammatory loop between Il-23 expression by TEC and IL-17 producing cells explaining the chronic inflammation in MG thymuses.

AUTO1-0113
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

IGG4 AUTOANTIBODIES AGAINST MUSCLE-SPECIFIC KINASE UNDERGO FAB-ARM EXCHANGE IN MYASTHENIA GRAVIS PATIENTS

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Background

Myasthenia gravis (MG) with antibodies to muscle specific kinase (MuSK-MG) is hallmarked by IgG4 antibody against MuSK that inhibit a pathway that clusters the acetylcholine (neurotransmitter) receptors and leads to failure of neuromuscular transmission. A key feature of IgG4 antibodies is the ability to exchange Fab-arms with other, unrelated, IgG4 molecules, making the IgG4 molecule potentially monovalent for the specific antigen. Whether pathogenic MuSK IgG4 is mono- or divalent for their antigen is unknown.

Method

In vitro Fab-arm exchange-inducing conditions were applied to MuSK antibodies in sera, purified IgG4 and IgG1-3 sub-fractions. Solid-phase cross-linking assays were established to determine the extent of pre-existing and inducible Fab-arm exchange. Functional effects of the resulting populations of IgG4 antibodies were determined by measuring inhibition of agrin-induced AChR clustering in C2C12 cells. To confirm the results, κ/κ, λ /λ and hybrid κ/λ IgG4s were isolated and tested for MuSK antibodies.

Results

At least fifty percent of patients had IgG4, but not IgG1-3, MuSK antibodies that could undergo Fab-arm exchange in vitro under reducing conditions, but there were also MuSK antibodies in vivo that were divalent (monospecific for MuSK). Fab-arm exchange with normal human IgG4 did not prevent the inhibitory effect of serum derived MuSK antibodies on AChR clustering in C2C12 mouse myotubes.

Conclusion

The results suggested that a considerable proportion of MuSK IgG4 could already be Fab-arm exchanged in vivo, and this was confirmed by isolating endogenous IgG4 MuSK antibodies containing both κ and λ light chains. These new findings demonstrate pathogenicity of Fab-arm exchanged antibodies.

AUTO1-0428
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

ALTERED NUMBER AND FUNCTIONALITY OF REGULATORY B CELLS IN MYASTHENIA GRAVIS PATIENTS

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Background

To date B cells have been considered to play a pathogenic role in myasthenia gravis (MG) due to their ability to produce autoantibodies targeting mainly the acetylcholine receptor (AChR). However, a small percentage of B cells possesses regulatory properties (Breg cells).

Method

We investigated the proportion and function of Breg cells in $AChR^+$ MG patients and analyzed the influence of MG treatments.

Results

PBMCs were analyzed for $CD19^+CD24^{++}CD38^{++}$ Breg cells by flow cytometry. We observed a significant decrease of Breg cells in MG patients. Analyzing patients before and after thymectomy, we showed a restoration of the proportion of Breg cells after thymectomy. In parallel, we observed the presence of Breg cells in thymic germinal centers. In contrast, in MG patients treated with corticosteroids, a more severe decrease of Breg cells was observed. Similarly dexamethasone reduced *in vitro* the number of Breg cells.

Breg cell function is based on their ability to produce IL-10. Upon PBMCs stimulation with CpG or CpG/CD40, a significant increase of $CD19^+IL\text{-}10^+$ cells and of the mean fluorescence intensity (MFI) for IL-10 was observed with control PBMCs. Using PBMCs from MG patients, the increase of $CD19^+IL\text{-}10^+$ cells was still observed but to a lesser extent and was not associated with an increase in IL-10 MFI.

Conclusion

In this study, we clearly demonstrated a decrease in the proportion and function of Breg cells in MG suggesting altered immunomodulatory mechanisms. If thymectomy restore the percentage of Breg cells, the effect of corticosteroids seemed detrimental for Breg cells despite their well-known anti-inflammatory properties.

AUTO1-0405
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

TH17/IL-23 TARGETED THERAPY IN A HUMANIZED MOUSE MODEL OF MYASTHENIA GRAVIS

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Background

Autoimmune Myasthenia Gravis (MG) is a neuromuscular disease mainly caused by auto-antibodies against the acetylcholine receptor ($AChR^+$). $AChR^+$-MG young patients display hyperplastic thymus with ectopic germinal centers. In addition, MG thymuses exhibit a chronic inflammatory state illustrated by dysfunctional regulatory T cells (Treg) while the pro-inflammatory T-cells (i.e. Th17 cells, $CD4^+CCR6^+IL23R^+$) are over-activated (Gradolatto et.al., 2014). We recently developed a humanized preclinical MG model into immune-deficient NSG mice (NSG-MG), and we could demonstrate that grafting thymic MG fragments could lead to the development of myasthenic symptoms (Sudres et.al., 2017), making this model relevant for testing new therapies

Method

The aim of the study was to evaluate the impact of blocking IL-23, a critical cytokine involved in Th17 cell differentiation, thymus inflammatory state and MG clinical course in the NSG-MG model.

Results

Our data show that engrafted human $AChR^+$ MG thymuses release a higher percentage of inflammatory T cells ($CD4^+CCR6^+$) and IgG in NSG-MG blood than control thymuses. Treatment of NSG-MG mice with a monoclonal anti-human IL-23p19 antibody decreased circulating IgGs, and $CD4^+CCR6^+$ inflammatory T-cells. More, RT-PCR analyses of engrafted human MG thymuses, after six weeks, showed a reduced expression of IL-17 in mice receiving the monoclonal antibody, although no improvement in the clinical symptoms (muscle force) was observed

Conclusion

Altogether these data suggest that anti-IL-23p19 decreases 1) the inflammatory state in $AChR^+$ MG thymuses by controlling Th17 cell differentiation 2) thymic IgG production. However, these changes appear insufficient to limit AChR antibody effects in the periphery and therefore to control the clinical symptoms

AUTO1-0819
MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE NEUROLOGICAL DISORDERS, MYASTHENIA GRAVIS

SUSAC'S SYNDROME: CLINICAL CHARACTERISTICS, CLINICAL CLASSIFICATION AND LONG TERM PROGNOSIS

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Introduction: Susac`s syndrome is a rare syndrome characterized by clinical triad of: CNS dysfunction, sensorineural hearing impairment and branch retinal artery occlusion (BRAO).
The purpose of this study was to examine the long term prognosis of patients with Susac's syndrome treated in our center.

Methods: Retrospective case series. Susac's syndrome patients treated between the years 1998–2014 were evaluated. Demographic data, neurological, hearing and ocular signs ,MRI findings, ocular characteristics, treatment and long term prognosis were recorded and evaluated.

Results: The series included 10 patients (4 male, 6 female) ,in the mean age of 38 years. Mean follow up time was 35 months.
20%of patients present with full triad. Seven patients developed a full triad during the follow up period. The average time to full triad was 7 months.

All patients were treated at diagnosis with a pulse of high dose intravenous methylprednisolone (1 gr/day). Improvement in visual acuity and visual field was noted at the end of the follow up time, yet the improvement was not statically significant (p= 0.479, 0.053 respectively, matched pairs). 5 patients (50%) had neurological damage at the end of the study. 5 patients (50%) had no improvement in hearing loss

Summary: Susac`s syndrome is a rare syndrome that can mimic other disorders. The diagnosis is challenging because most of the patients do not initially present with the tried. We suggest a clinical classification for the syndrome that may assist in early diagnosis of the syndrome. Early diagnosis may lead to better prognosis in those young patients

AUTO1-0022
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

REFLEX TESTING OF SPECKLED CYTOPLASMIC PATTERNS OBSERVED IN ROUTINE ANA HEP-2 INDIRECT IMMUNOFLUORESCENCE WITH A MULTIPLEX ANTI-SYNTHETASE DOT-BLOT ASSAY: A MULTICENTER PILOT STUDY

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Background

Immunofluorescence on HEp2-cells is the standard diagnostic assay for the detection of anti-nuclear antibodies (ANA). Cytoplasmic speckled patterns are a common finding, and are associated with various antibodies, including anti-synthetase antibodies. Moreover, anti-synthetase syndrome is increasingly recognized as a pleomorphic entity, possibly presenting as isolated arthritis or interstitial lung disease.

Method

Sera referred for routine ANA testing were selected on the basis of the presence of a fine dense speckled cytoplasmic pattern (254 samples) and compared to control sera with negative cytoplasm (239 samples). All 493 samples were tested with a commercial synthetase profile dot-blot (D TEK - Alphadia-Alifax) including anti-Jo1, -PL7, -PL12, -EJ, -OJ, -KS, -ZO, -HA, -SRP and -Ribosome P0. Retrospective clinical data was searched for positive patients.

Results

Dot-blot identified 18/254 (7.1%) positive sera in the samples with a cytoplasmic fluorescence pattern and 4/239 (1.7%) in the control group ($\chi 2=8.4627$; $p=0.0036$). Blot intensity was more intense in samples with concordant cytoplasmic staining (cytoplasmic negative 27 ± 12.4; cytoplasmic positive 53.9 27 ± 27.7; p=0,0027). In the positive samples 8/18 had a highly compatible IIM diagnosis, 7/18 an uncharacterized connective tissue disease, and 3 a diagnosis not associated with the presence of anti-synthetase antibodies.

Conclusion

This algorithm enabled the identification of a significant quota of patients with rare anti-synthetase antibodies and an incomplete or atypical clinical picture. Reflex testing strategies of speckled cytoplasmic patterns with multiplex assays containing cytoplasm-specific antigens, as opposed to standard ENA testing, may yield important data and for this reason should be implemented in routine ANA testing.

AUTO1-0546
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

EVALUATION OF CTD SCREEN IN THE DIAGNOSIS OF CONNECTIVE TISSUE DISEASES IN A POST-MENOPAUSAL POPULATION, THE CAMARGO COHORT

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Background

Autoantibodies are important in the diagnosis of Connective Tissue Diseases (CTD). Most CTD are diagnosed in early-middle age women. However, the order of autoimmune testing has increased for elderly population in the last years. We aim to study the prevalence and clinical relevance of anti-nuclear antibodies (ANA) in a post-menopausal non-selected cohort from General Practice (GP).

Method

2943 patients, with 9 years of clinical follow-up, from a GP Cohort (Camargo, Cantabria, Spain) were included in the study. One serum patient at inclusion was analyzed for the presence of ANA by immunofluorescence (IFA) on HEp-2 cells (Biosystems, Spain) and CTD Screen (Thermo Fisher, Germany), using cut-off values recommended by manufacturer.

Results

631 (27.2%) subjects were ANA positive by IFA (138 at titers >1/640). 279 (10%) were CTD Screen positive (Table 1). The best agreement between both methods was for high IFA titers with homogeneous and granular patterns. 100% of anti-centromere antibodies by IFA were detected with CTD Screen. However, less than 20% of sera with cytoplasmic or nuclear dots patterns were CTD Screen positive. Considering the clinical diagnosis after 9 years of follow-up, none of the CTD Screen + / IFA- patients were suspected or diagnosed of CTD. Less than 10% of CTD Screen + patients were evaluated at our CTD devoted clinic.

Table 1. Results of CTD Screen and ANA by IFA

CTD Screen	ANA IFA	n
+	+	133
+	-	146
-	+	630
-	-	1871

Conclusion

The study of serum autoantibodies in elderly subjects with a low pre-test probability must be interpreted with caution and cut-off values must be age and genderly adjusted.

AUTO1-0552
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

THE IMPORTANCE OF ESTABLISHING A CUT-OFF POINT ADJUSTED TO DEMOGRAPHICS IN THE LABORATORY TEST FOR DIAGNOSING AUTOIMMUNE RHEUMATIC DISEASES

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Background

Serum autoantibodies are important in the diagnosis of Autoimmune Rheumatic Diseases (ARD). Most of ARD are diagnosed at early-middle age, and cut-off points for positive results have been established with young patients and healthy controls. However, nowadays the order of autoimmune testing has increased in elderly population. We aim to study the prevalence of anti-nuclear (ANA) and anti-cyclic citrullinated peptides (CCP) antibodies in a post-menopausal cohort from General Practice (GP).

Method

3030 patients from GP Cohort (Camargo, Cantabria, Spain), with 9 years followed-up, were included in the study. Sera sampled from 2943 patients at inclusion time were analyzed. Presence and levels of ANA and anti-CCP antibodies was analyzed by immunofluorescence (IFA) on HEp-2 cells (Biosystems, Spain), Bioplex 2200 ANA Screen, and Bioplex 2200 anti-CCP (Biorad, USA), respectively.

Results

Cut-off values recommended by manufacturer for Bioplex and 1/160 for IFA were used. 631 (27.2%) subjects were ANA positive by IFA and 400 (15.4%) by Bioplex (Table 1). Bioplex was mainly positive due to anti-RNP and anti-dsDNA antibodies. 90.2% of Bioplex+/IFA- patients did not develop any manifestation of ARD after 9 years of follow-up and only one had SLE and three rheumatoid arthritis (RA). 15 subjects were diagnosed with organ-specific autoimmune diseases. For anti-CCP antibodies, 63 (2.15%) patients were positive. However, only 19/63 patients were diagnosed of RA after follow-up. Specificity of results increased when cut-off values were adjusted.

Table 1. Results of Bioplex 2200 ANA Screen and ANA by IFA

Bioplex ANA Screen	ANA IFA	n
+	+	160
+	-	235
-	+	664
-	-	1721

Conclusion

The establishment of cut-off values for true positive results for serum autoantibodies with new methods, such as Bioplex, is of special relevance in unselected population.

AUTO1-0516
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

MULTI SEROLOGY TESTING IN RHEUMATOID ARTHRITIS: HOW TO MAXIMISE DIAGNOSTIC PERFORMANCE?

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Background

Rheumatoid arthritis (RA) diagnosis requires a combination of clinical, laboratory and imaging investigations, and it is known that the detection of antibodies to cyclic citrullinated peptides (CCP) and to Rheumatoid Factor (RF) may occur long before the onset of RA symptoms. In RA, the consequences of wrong serology test results are particularly important: False Positive results are managed as RA patients bringing about extra costs until correct diagnosis is made, while False Negatives receive further investigations and treatment delayed in time, allowing for disease progression.

The aim of the present study was to evaluate the combined diagnostic performance of EliA RF-IgA, EliA RF-IgM, and EliA CCP, used alone or in combination.

Method

Data available in house including 190 established RA patients and 197 controls (either affected by other conditions or healthy donors) was used to assess the diagnostic performance of multi-serology testing.

Results

The diagnostic performance was:

- RF-IgA: sensitivity [95%CI]=40.5% [33.5%-47.9%], specificity=92.4% [87.8%-95.7%];

- RF-IgM: sensitivity=59.0% [51.6%-66.0%], specificity=89.3% [84.2%-93.3%];

- CCP: sensitivity=59.5% [52.1%-66.5%], specificity=96.5% [92.8%-98.6%].

Defining a “positive result” as “positivity to at least one test” increased sensitivity; “positivity to all the tests” increased specificity:

- using both RF-IgA and RF-IgM led to 95.9 [92.2-98.2] specificity,

- adding CCP to RF-IgM increased specificity to 99.5 [97.2-100];

- the 3 tests together maximized specificity (100% [98.1-100]), reducing sensitivity.

Conclusion

Results show that multi-serology testing can improve diagnostic accuracy of the individual RF IgA, RF IgM and CCP tests. Consequently, their combined usage demonstrates superior value from patient and payer perspective.

AUTO1-0680
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

A MULTI-CENTRE STUDY FOR STANDARDIZATION OF ANTINUCLEAR ANTIBODY INDIRECT IMMUNOFLUORESCENCE SCREENING WITH AUTOMATED SYSTEM

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Background

Indirect immunofluorescence assay (IFA) using HEp-2 as substrate plays a consolidate role for the detection and measurement of ANA, which is currently considered as the reference method for detection. Manual operation is still very common in China, therefore, the need of standardization and automation for ANA-IFA detecting has been highlighted.The current multi-center study is aimed to evaluate if HELIOS contributes to comparability of ANA screening results among different labs, and establish application specification of HELIOS for standardization of ANA detection.

Method

ANA detection by manual IFA method and HELIOS on 230 clinical serum samples in eight laboratories. The performance to discriminate positive/negative screening results, endpoint titer estimation and pattern recognition were evaluated in HELIOS and manual visual.

Results

The positive coincident rate for ANA detection by manual IFA ranges from 87.7% to 97.8%, the negative coincidence rate ranges from 68.8% to 100%, the correctly estimated titer evaluation were 80 to 171 cases, the correct pattern in 146 to 161 cases, respectively. The positive coincident rate of HELIOS for ANA detection ranges from 91.2% to 97.7%, the negative coincidence rate ranges from 96.5% to 100%, the correctly estimated titer evaluation were 145 to 157 cases, the correct pattern in 123 to 140 cases, respectively.

Conclusion

HELIOS could provide accurate diagnostic results, this include not only positive/negative results, but also endpoint titer, common patterns. The application of this system can help to promote standardization of ANA detection.

AUTO1-0565
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

AUTOANTIBODIES IN TYPE 1 DIABETES: EVALUATION OF FIVE YEARS EXPERIENCE AS A REFERENCE CLINICAL LABORATORY

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Background

Type 1 diabetes (DM1) is a condition characterized by a lack of insulin due to autoimmune processes that destroy the insulin-producing beta cells in the pancreas whilst type 2 diabetes is primarily associated with insulin resistance.

Diabetes-related autoantibody testing is primarily used to help distinguish DM1 from diabetes due to other causes. The first antibodies described in association with the development of DM1 were Islet Cell Autoantibodies (ICA). Afterward, antibodies to Insulin (IAA), Glutamic Acid Decarboxylase (GAD65) and Protein Tyrosine Phosphatase (IA2) have been defined.

Method

The authors present a 5 years revised casuistic as a reference clinical laboratory center in autoimmune disease and DM1 diagnosis.

Results

Autoantibodies against GAD65 are found in 80% of DM1 at clinical presentation. Presence of ICA and IA2 at DM1 range from 69-90% and 54-75%, respectively. IAA is usually the first marker in young children at risk for diabetes.

The common performance of ICA assay showed a median sensitivity and specificity of 81% 96%, respectively. Both GAD65 and IA2 immunoassays were found to have high sensitivity (80 and 58%) and specificities (90 and 100%, respectively). The IAA assay ranged in sensitivity from 4-42%. Overall, standardization of IAA and ICA assay continues to be more challenging than GAD65 or IA2.

Conclusion

Autoantibodies can diagnose atypical diabetes and predict disease set-up in normoglycemic relatives of DM1 subjects. Predictive value of the combined presence of ICA, IAA, GAD65 and IA2-A is 100%.

AUTO1-0473
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

COMPREHENSIVE AUTO-ANTIBODY INVESTIGATION OF PSYCHIATRIC DISORDER ON HIGH-DENSITY PROTEIN MICROARRAY PLATFORMS

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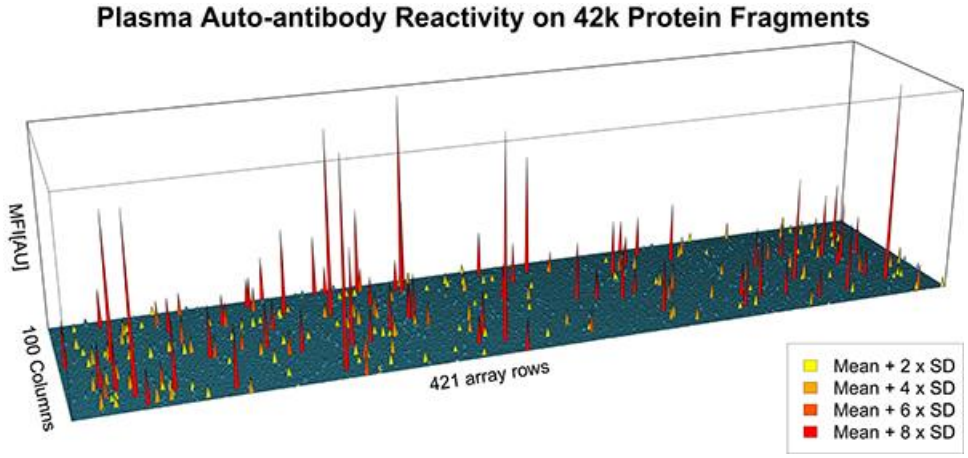
Background

In a recent study we used a targeted affinity proteomics approach to investigate the autoantibody reactivity in patients with psychotic features, such as anxiety and compulsive disorders, in an attempt to identify disease associated biomarkers. In this study we focus on a subgroup of patients with compulsive disorder to further investigate and characterize their autoantibody reactivity.

Method

We have utilized high-density protein microarrays for analysis of 12 samples of patients with compulsive disorder. Initially we used in-house produced protein microarrays with 42.100 recombinant protein fragments from the Human Protein Atlas, representing approximately 19.000 Ensembl Gen IDs. Additionally, subsets of samples have been analysed on two commercially available alternatives; the HuProt™ array (CDI Laboratories Inc. (>20.000 full-length proteins, representing 16.152 genes)), and the ProtoArray® Human Protein Microarray (ThermoFisher Scientific (> 9.000 full-length proteins).



Results

We could confirm a previous finding of autoantibodies against Annexin A2 among a subset of six samples and identify several new possible autoreactive antigens in the subgroup of patients with compulsive disorder. We could also determine that the different platforms complemented each other as each platforms contained targets that were uniquely detected.

Conclusion

By characterizing the autoimmune reactivity of this patient group we can gain insights into the autoantigens associated to compulsive disorder and investigate the biological function of these autoantigens for compulsive disorder. We intend to further investigate our findings by the use of additional full-length protein microarrays to make an even more in-depth analysis for these samples, and if possible also epitope map the targets using peptide arrays.

AUTO1-0407
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

AN ANA SCREENING ASSAY CONTAINING MULTIPLE ANTIGENS INCREASES THE SENSITIVITY AND SPECIFICITY OF ANA TESTING BY INDIRECT IMMUNOFLUORESCENCE

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Background

Indirect immunofluorescence (IIF) on Hep-2 cells is considered the gold standard for screening of antinuclear antibodies (ANA). However, while being sensitive the method lacks specificity.

Method

To investigate the diagnostic usefulness of an ANA screening assay containing most of the diagnostically relevant antigens sera from 265 consecutive patients presenting with symptoms characteristic of a connective tissue disease (CTD) were analysed by both IIF and the EliA® CTD Screen (Thermo Fisher Scientific).

Results

Ninety patients were positive by IIF and 78 by CTD Screen; 61 sera were positive in both systems, 17 only in the CTD Screen and 29 only in IIF. In all double positive patients at least one diagnostically relevant antibody was detected. In addition to the antibodies determined by standard routine diagnostics antibodies to ribP, RNA polymerase III and Pm/Scl were detected. Importantly, antibodies were also detected in 15 of the 17 patients exclusively positive in the CTD Screen including anti-dsDNA, anti-Ro60/SSA, anti-U1snRNP, anti-La/SSB and anti-Jo-1. However, among the 29 sera exclusively positive by IIF only two contained a diagnostically relevant antibody. Clinical evaluation suggested that the majority of CTD Screen pos/IIF negative patients were at high risk for developing a CTD, particularly primary Sjogren´s syndrome. Most common symptoms were arthalgia (n=13), sicca syndrome (n=12) and Raynaud´s phenomenon (n=5).

Conclusion

CTD screening assays containing multiple antigens seem to be useful and highly specific diagnostic tools that increase sensitivity of ANA testing which may enable the physician to diagnose and treat “ANA negative” connective tissue diseases at an earlier stage.

AUTO1-0384
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS OF AUTOIMMUNE DISEASES

EVALUATION OF A NEW M23 ISOFORM-BASED ELISA ASSAY FOR ANTI-AQUAPORIN 4 AUTOANTIBODIES: ANALYTICAL PERFORMANCE AND CLINICAL CORRELATION

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Background

Several assays have been developed to detect anti-aquaporin-4 (AQP4) antibodies. However, many of these assays require sophisticated techniques and are thus only available at specialized laboratories.
The aim of this study was to evaluate the analytical and clinical performance of a new commercial enzyme-linked immunosorbent assay (ELISA RSR, AQP4 Ab Version 2) to detect anti-AQP4 antibodies on a fully automated system (SkyLAB 752, DASITGroup, Milan, Italy).

Method

Serum samples from 64 patients with neuromyelitis optica spectrum disorders (NMO-SD) (NMO, longitudinally extensive myelitis-LETM, optical neuritis, myelitis) and 27 controls were tested for anti-AQP4 antibodies. All sera were previously tested using an indirect immunofluorescence (IIF) methods on primate tissue. Commercial control sera were used to determine within-run, between-day and within laboratory precision (CLSI guidelines).

Results

The within-laboratory CV were 8.2% and 8.0% at the concentrations of 12.4 and 28.1 U/mL, respectively. At a cut-off value >2.1 U/mL, the sensitivity and specificity for NMO were 83.3% and 100%, respectively. The ELISA assay provided 100% concordant results with IIF. The median concentration of anti-AQP4 antibodies was statistically higher in patients with NMO than in patients with other NMOSD and in controls (Kruskal Wallis test, $P < 0.0001$). In particular, the median concentration of anti-AQP4 antibodies was statistically higher in patients with NMO than in patients with LETM ($P = 0.0006$).

Conclusion

This new ELISA assay performed on a fully automated system, showed a high sensitivity and absolute specificity, a very good within-run and within-laboratory CV and provided observer-independent quantitative results.

AUTO1-0894
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

GLYCOSYLATION ALTERATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATHOGENESIS

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Systemic Lupus Erythematosus (SLE) is one of the most challenging autoimmune diseases for clinicians as it may be presented as a severe, relapsing and disabling immune-mediated disorder affecting multiple organs and still remaining incurable1. N-glycosylation is an essential post translational modification that participates in the correct recognition of cells by the immune system2. In this study we have been addressing whether an incorrect N-glycosylation is associated with loss of tolerance in an autoimmune context3. Accordingly, we analysed the profile of N-glycosylation of a subset of biopsy-proven lupus nephritis from SLE patients and normal kidney tissue. We observed a significant decreased expression of a specific glycans structure in the renal parenchyma, namely a decreased expression of complex branched N-glycans (Figure 1A), when compared to healthy kidney. Complementary, the levels of gene expression of the enzyme responsible for the synthesis of these complex structures, MGAT5, was also diminished in T lymphocytes from SLE patients' blood.
We have demonstrated for the first time in SLE, glycosylation is a regulatory mechanism that tips the balance between homeostasis/self-tolerance and autoimmunity opening a potential novel targeted-specific mechanism in SLE pathogenesis.
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AUTO1-0890
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

THE NOTCH PATHWAY IN THE MICROVASCULAR ENDOTHELIUM OF SYSTEMIC SCLEROSIS

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Microvascular dysfunction occurs early in systemic sclerosis. We explore changes in endothelial Notch signaling in systemic sclerosis, which has a central role in the regulation of microvascular remodeling, its interaction with perivascular structures and immunology.

AUTO1-0893
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

CHOREOGRAPHING IMMUNITY AND TOLERANCE INDUCTION IN THE THYMUS

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The development of vaccines for the treatment of infectious diseases, cancer and autoimmunity depends on our knowledge of T-cell differentiation. This proposal is focused on studying the thymus, the organ responsible for the generation of T cells that are responsive against pathogen-derived antigens, and yet tolerant to self. Within the thymus, thymic epithelial cells (TECs) provide key inductive microenvironments for the development and selection of T cells that arise from hematopoietic progenitors. As a result, defects in TEC differentiation cause syndromes that range from immunodeficiency to autoimmunity, which makes the study of TECs of fundamental, and clinical, importance to understand immunity and tolerance induction. I will discuss current projects on the development of this specialized cell subset and its role in choreographing immunity and tolerance induction.

AUTO1-0888
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

VITAMIN D STATUS IN PORTUGUESE AUTOIMMUNE PATIENTS

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Autoimmune disease onset is believed to result from a combination of environmental and genetic factors. Epidemiological and experimental evidence suggests that high levels of vitamin D, a known immunomodulator, may decrease the risk of several autoimmune diseases. A number of studies have shown that Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE) patients have lower levels of 25-hydroxyvitamin D than healthy populations.
Two cross-sectional studies were conducted in 262 patients with MS and 124 patients with SLE from the outpatient clinic of CHP-HSA. The control group comprised 198 healthy individuals (HC) from the same geographic region.
Vitamin D serum levels were significantly lower in patients with MS (40.1±22.4 nmol/l, $p<0.0001$) and in patients with SLE (48.9±27.2 nmol/L, $p<0.001$) compared to healthy individuals (55.8±24.0 nmol/l). Concerning disease severity a statistically significant inverse correlation was observed between Vitamin D levels and EDSS and MSSS scores ($p=0.001$) in MS patients. In SLE, patients with three or more flares had significantly lower 25(OH)D baseline levels ($p=0.004$).
Our results add to the growing body of evidence that lower levels of Vitamin D are associated with higher risk and increased disease activity in MS and SLE. Whether Vitamin D has a causal role in this association remains an open question that will be addressed in undergoing interventional studies.

AUTO1-0896
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

GLYCANS AS NOVEL IMMUNOMODULATORS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Idiopathic inflammatory myopathies (IIM) remain a major clinical challenge worldwide. The precise aetiopathogenesis of this chronic and disabling disorder remains elusive which precludes the development of novel and effective therapeutic strategies. Moreover, classification is still not consensual and the therapeutic guidelines do not exist, with treatment being mainly empirical and not targeted-specific. Finally, meaningful prognostic factors are missing.
Glycosylation alterations both in physiological and pathological immunology are being unravelled and, in some autoimmune diseases, such us ulcerative colitis, recent studies are paving the way for new disease mechanisms, biomarkers and therapeutic targets. We are addressing the clinical impact of glycosylation alterations as a new disease mechanism in IIM, envisioning the identification of key prognostic biomarkers and specific targets for future therapeutic trials.

AUTO1-0887
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

IMMUNE TOLERANCE IN PREGNANCY

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During pregnancy, maternal immune system is challenged to tolerate a semiallogenic fetus in order to achieve a healthy newborn. In this paradigm, the placenta is the real “transplant”, and the pathogenesis of miscarriage, pre-eclampsia, preterm birth and some cases of fetal growth restriction results from abnormal trophoblast growth and differentiation, at any time after the early stages of implantation. This essential trophoblast invasion needed to the development of a fully functional placenta demands an intricate network of immune tolerance that allows the growth of cells with paternal antigens through the maternal decidual. Several mechanisms with diverse protagonists are involved in this complex tolerance game. We will explore the importance of T regulatory cells and the ratio Tregs : Th17 lymphocytes in this scenario and according to our results with lupus pregnant patients.

AUTO1-0897
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

A NOVEL ROADMAP OF MEDULLARY THYMIC EPITHELIAL CELL DIFFERENTIATION

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The thymus is the primary lymphoid organ essential for T cell differentiation. This process depends on thymic epithelial cells (TEC) that provide specialized microenvironments for T cell development and selection. In particularly, medullar TECs (mTECs) are central to orchestrate later stages of T cell differentiation, including negative selection, T regulatory cell differentiation and single positive thymocyte maturation. mTECs are heterogeneous with regard to the expression of MHC-II and CD80, defining prototypical mTEClo(MHCIIlowCD80low) and mTEChi(MHCIIhighCD80high) subsets. Although initially considered as immature and mature stages, these subsets hide a further degree of heterogeneity as shown by the identification of Claudin3+SSEA1+ mTEC precursors, Ccl19/Cll21+ cells, which regulate the migration of positively selected thymocytes into the medullar space and reside within mTEClo, and Aire+ and Fezf2+ cells, which are essential to the establishment of central. Yet, it remains elusive the lineage and functional relationship between these different mTEC populations. Furthermore, there is not a reliable set of cell surface markers to allow the rapid mapping of the different mTEC subpopulations. Combining integrative multicolour flow cytometry analysis, in vitro thymic organotypic cultures and in vivo thymus transplantation, we identify novel mTEC subsets and we will present experimental evidence on their lineage and functional properties.

AUTO1-0899
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

T-CELL REGULATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Foxp3+ T-regulatory cells (Tregs) of Systemic Lupus Erythematosus (SLE) patients are functionally deficient in an IL-2 related manner, which is best reflected by reduced surface expression of the IL-2 receptor CD25 that can reportedly be corrected by low-dose IL-2 therapy. We have characterized this CD25 deficiency in detail, discovering that it was principally shared by SLE patients and unaffected relatives on early Tregs, but strongly maintained upon Treg activation only in manifest SLE patients while unaffected relatives compensated initial CD25 reduction by peripheral upregulation1,2. In SLE patients studied longitudinally, this CD25 upregulation was found indicative for a characteristically altered dynamic turnover of Treg as well as T-helper cells. This alteration includes a surprising instability of activated Treg frequencies over time, with individual degrees of fluctuation strongly correlated to individual disease activity, IgG anti-dsDNA and lymphopenia. Clonal analysis further suggests that this dynamic alteration, in a context with SLE-associated lymphopenia, can drive temporary expansions of pathogenic T-helper clones3. We hypothesize that such expansions, due to destabilized T-cell regulation, may be a key factor triggering disease flares in SLE.

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AUTO1-0900
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

EPIGENETIC MARKERS IN AUTOIMMUNE PORTUGUESE PATIENTS

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Autoimmune diseases (DAI) have a complex pathogenesis in which genes and environmental factors are involved. An increasing number of studies have revealed that epigenetic mechanisms contribute to the pathogenesis of these diseases, and may also play a role in disease development. MicroRNAs (miRNA) are small noncoding RNA molecules that function as posttranscriptional regulators of gene expression, controlling different biological processes having a significant impact on the immune system homeostasis. In SLE, for example, miR-146a dysregulation is associated with altered IFN responses and Treg function. Knowing that miRNA expression is very stable in biological fluids such as plasma or serum our aim was to evaluated miRNA expression in serum of autoimmune patients.
Using real-time polymerase chain reaction analysis, the miR-146a and miR-155 expression levels were assessed in serum from 81 DAI patients (58 SLE and 23 Behçet patients) and 78 healthy controls. The miR-146a expression level was significantly decreased in SLE (4 fold) and Behçet disease patients (3 fold) compared to the healthy controls. Our results also evidence an association between low miR-146a levels and disease activity in SLE (7 fold lower in patients with SLEDAI≥4) and disease severity in Behçet patients (5 fold lower in patients with uveitis). Conversely, miR-155 serum levels were upregulated in both DAI cohorts.
These preliminary results from a Portuguese cohort, are in accordance with other studies highlighting the important role played by miR-146a and miR-155 in the pathogenesis of DAI. The fact that these molecules could be easily and reliably assessed in serum, suggests that they could be suitable biomarkers for DAI diagnosis and progression. To clarify its effective contribution further studies are warranted.

AUTO1-0892
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

TURNING SWEET IN AUTOIMMUNITY. GLYCOSYLATION ALTERATIONS AS A NEW MECHANISM IN THE LOSS OF IMMUNETOLERANCE WITH CLINICAL APPLICATIONS

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The immune system is guided by a series of co-stimulatory and co-inhibitory pathways. The disruption of the control of these molecular checks and balances leads to a breakdown of self-tolerance and thus to unpredictable inflammatory and autoimmune states. The mechanisms underlying the genesis of this loss of immunological tolerance are still elusive and autoimmune diseases remain incurable and life-threatening disorders with incidence increasing worldwide. Although underappreciated for many years, exciting findings by others and us have been underscoring the essential contributions of cell surface glycosylation in immune tolerance and in the pathogenesis of autoimmunity. We have been contributing to elucidate how glycosylation integrates the regulatory networks that govern the innate and adaptive immune responses accounting for autoimmunity, as an exciting and innovative approach on investigating the pathophysiology of immune-mediated disorders.

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AUTO1-0895
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

GLYCOSIGNATURE OF APOPTOTIC CELL-DERIVED MICROPARTICLES IN SYSTEMIC LUPUS ERYTHEMATOSUS: POTENTIAL BIOMARKER OF DISEASE?

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by multiple clinical manifestations. It has been hypothesized that improperly cleared apoptotic debris could constitute a source of autoantigens capable of triggering SLE. Microparticles (MPs) are products of dying cells that can provide an important source of bioactive molecules that can induce a wide range of immunological effects. Apoptotic cells and MPs are known to expose “eat-me” signals and other potential antigens like altered glycoepitopes important for clearance and immunopathogenesis of the disease. In this study we analyzed the glycosignature of apoptotic cell-derived MPs isolated from the blood of a well characterized cohort of SLE patients and compared these glyco profiles to those of individually matched population controls.
We have observed a unique profile of high mannose N-glycans and complex branched N-glycans by both flow cytometry and western blot detection of glycoproteins in circulating apoptotic MPs from SLE patients comparing with healthy controls. Moreover, the relationship between the glycosylation profile of MPs and the clinical/prognostic features of SLE was evaluated.
The determination of the glycosignature of MPs can elucidate novel mechanisms underlying the loss of immunotolerance that characterizes SLE with promising clinical and prognostic applications.

AUTO1-0898
NEDAI SESSION- NOVEL INSIGHTS INTO THE MECHANISMS UNDERLYING THE LOSS OF IMMUNETOLERANCE IN AUTOIMMUNITY: THERAGNOSTIC APPLICATIONS

IMBALANCE OF BLOOD TFH AND TFR CELLS IN SYSTEMIC AND ORGAN-SPECIFIC HUMAN AUTOIMMUNITY

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Many autoimmune diseases are mediated by self-reactive antibodies produced during disturbed B-T cell interactions in the germinal center (GC). T follicular helper (Tfh) cells and T follicular regulatory (Tfr) cells are key players regulating GC reactions: while Tfh cells support the production of high-affinity antibodies, Tfr cells limit the production of self-reactive antibodies. Therefore, the balance between Tfh and Tfr cells have a significant impact on GC outcome. While targeting B or T cells is effective in treating autoimmune diseases, therapies directly targeting GC are still missing. We have recently found that the balance between circulating Tfh and Tfr cells is altered in human systemic autoimmunity. In order to investigate whether such dysregulation is also observed in organ-specific autoimmunity, we compared Sjögren Syndrome (SS) and Hashimoto's Thyroiditis (HT) patients.
We analyzed peripheral blood Tfh and Tfr cells of those two distinct autoantibody-mediated autoimmune diseases. We found a significant increase in Tfr/Tfh ratio in peripheral blood of SS patients compared to age-matched healthy donors, contrary to HT patients where a considerable decrease in Tfr/Tfh ratio was observed. These results suggest SS and HT do not share common mechanisms of GC dysregulation. However, circulating Tfh cells in both diseases expressed GC-related activation markers, suggesting greater Tfh cell activation in autoimmune patients regardless of the underlying disease.
Our results show SS and HT are characterized by dysregulation of Tfh/Tfr ratio possibly implicated in the loss of self-tolerance and emergence of autoantibodies. However, imbalance of circulating Tfr and Tfh cells is distinct in these diseases: SS, a systemic autoimmune disease, has higher Tfr/Tfh ratio, while HT, an organ-specific autoimmune disease, displays a lower Tfr/Tfh ratio. Although further studies are needed to validate the significance of Tfr/Tfh ratio in other autoimmune diseases, blood Tfr/Tfh ratio may constitute a novel biomarker for autoantibody-mediated autoimmunity, potentially identifying patients with greater benefit for therapeutic approaches targeting B-T cell interactions.

AUTO1-0465
NEURONAL AUTOIMMUNE DISEASES

PANDAS/BASAL GANGLIA ENCEPHALITIS AUTOANTIBODIES AND THE BLOOD-BRAIN BARRIER

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Background

Streptococcus pyogenes infections are associated with two autoimmune diseases of the nervous system: the movement disorder Sydenham's chorea and the neuropsychiatric syndrome PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections). This bacterium induces autoreactive, mimetic antibodies against several targets in the CNS and other tissues. How such autoreactive antibodies cross the blood-brain barrier, however, is unknown for both PANDAS and other, more common autoimmune encephalitides such as anti-NMDA receptor encephalitis.

Method

We investigated: 1) whether sera from a cohort of 14 PANDAS patients at acute and convalescent stages recognize epitopes on human brain endothelial cells *in vitro*, in either a resting or inflamed state; 2) whether PANDAS sera influence the barrier properties of iPSC (induced pluripotent stem cell)-derived brain microvascular endothelial cells (BMECs); and 3) the presence of anti-D1R and anti-D2R (dopamine receptor) autoantibodies using a quantitative "On-Cell Western" assay (LI-COR) that maintains the extracellular domains of the human receptor proteins in their native conformation.

Results

Our results demonstrate anti-dopamine receptor autoantibodies in a subset of PANDAS patients, but no direct effect of autoantibodies on barrier permeability *in vitro*.

Conclusion

These data further support our earlier results from a mouse PANDAS/Sydenham's chorea model, that the initiating insult to the brain during these and other autoimmune encephalitides is likely to be Th17 cell entry that induces barrier breakdown, and thereby provides autoantibodies access to the CNS.

AUTO1-0724
NEURONAL AUTOIMMUNE DISEASES

HEARING LOSS IN AUTOIMMUNE DISORDERS: PREVALENCE AND THERAPEUTIC OPTIONS

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Background

The objective of this study was to review our current knowledge relative to the correlation between sensorineural hearing loss (SNHL) and autoimmune diseases, focusing on the prevalence of hearing loss in different pathologies and possible therapeutic approaches.

Method

A review of the literature on hearing loss in different forms of autoimmune disease has been carried out, with emphasis on incidence and prevalence of SNHL. Therapeutic protocols have been assessed including both conservative medical and rehabilitative methods. Cochlear implant outcomes have been investigated.

Results

The prevalence of hearing loss in autoimmune and immune-mediated inner ear diseases, as referred by case reports or single-center statistics, is widely variable. More difficult is the evaluation of severe/profound SNHL, usually reported in relation to cochlear implantation. Though these patients represent ideal candidates for cochlear implantation, as they become deaf after years of hearing; the associated systemic disease, the specific damage on inner ear structures and the medication taken may influence the result of cochlear implantation.

Conclusion

The main problem is the cochlear fibrosis or ossification that has been found to affect 50% of implanted ears in patients suffering from autoimmune and immune-mediated SNHL. Hence, in the presence of severe/profound SNHL earlier implantation may be indicated before post-inflammatory obliterative changes to the cochlea.

AUTO1-0189
NEURONAL AUTOIMMUNE DISEASES

LOW ALBUMIN LEVEL IS ASSOCIATED WITH POOR INITIAL RESPONSE TO IMMUNE THERAPIES IN AUTOIMMUNE ENCEPHALITIS

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Background

There is no known biomarker that predicts the response to immune therapy in autoimmune synaptic encephalitis. The use of a biomarker would aid in the decision to wait or adopt further immune therapies. Thus, we investigated serum albumin as a prognostic biomarker to predict the treatment response of early immune therapies in patients with autoimmune encephalitis.

Method

We enrolled patients who were diagnosed with definite autoimmune limbic encephalitis and underwent IVIg treatment at Seoul National University Hospital from 2012 to 2017. Patients were dichotomized according to serum albumin prior to IVIg administration with a cut-off level of 4.0 g/dL, which was the median value of 50% of patients.

Results

Seventeen (53.1%) of the 32 patients with definite autoimmune encephalitis who received IVIg treatment in our hospital had low serum albumin (<4.0 g/dL). The initial disease severity (mRS≥4) was the sole factor that predicted low albumin in autoimmune encephalitis patients using multivariate analysis (P=0.013). The low albumin group exhibited a worse response to immune therapy at the third and fourth weeks from IVIg administration (P<0.01 and P=0.012, respectively), and recovery to activities of daily life without assistance was faster in the high albumin group (log-rank test for trend, P<0.01).

Conclusion

Our study found that pretreatment low serum albumin was a significant indicator of autoimmune encephalitis prognosis in the short-term and long-term. Further studies are necessary to validate the clinical implication of serum albumin in the treatment of autoimmune encephalitis.

AUTO1-0025
NEURONAL AUTOIMMUNE DISEASES

COGNITIVE DEFICITS IN A MURINE MODEL OF LUPUS AND EFFECTS OF THERAPEUTIC PEPTIDE P140

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Background

Lupus is frequently accompanied by behavioral deficits of unknown etiology, which are severe complications of the illness with no specific treatment. The aim of this study was to characterize the neurobehavioral outcomes of MRL/lpr mice, which develop an accelerated form of lupus-like disease, and to evaluate the effects of P140, a therapeutic phosphopeptide developed in our laboratory, on these defects.

Method

Motricity, anxiety-like behavior and cognitive function (T-maze alternation; task known for its sensitivity to hippocampal damage) have been evaluated in 60 female MRL mice (30 MRL/lpr and 30 $MRL^{+/+}$ -used as controls- treated or not with P140). The serum levels of several cytokines were measured by ELISA, and at sacrifice, brain and spleen were collected and used for flow cytometry evaluation to check cellular infiltration.

Results

Neither overt manifestations (dermatitis, alopecia) nor premature deaths were seen. Compared to 17-week-old $MRL^{+/+}$ controls, MRL/lpr mice display splenomegaly and increased proteinuria (normalized by P140), reduced brain weight (indicative of brain atrophy), and cerebral infiltration of lymphoid cells and macrophages. They show diurnal hyperactivity but no sensorimotor deficit nor clear-cut anxiety-like signs. However, we found that they are significantly impaired in alternation behavior, likely reflecting a hippocampal failure. This defect was totally compensated by P140 administration.

Conclusion

Collectively, these data are in line with the view that hippocampal neurodegeneration, at least impaired hippocampal function, accompanies lupus disease. They also demonstrate that the peptide P140 exerts central effects with cognitive expression, and arouse hope for patients suffering from neurolupus for which there is nowadays no specific treatment.

AUTO1-0638
NEURONAL AUTOIMMUNE DISEASES

BRAIN CELLS REACTIOINS TO ANTIGENS AND POSSIBLE AFFERENT PATHWAYS FROM IMMUNE SYSTEM TO CNS

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Background

BRAIN CELLS REACTIONS TO ANTIGENS AND POSSIBLE

AFFERENT PATHWAYS FROM IMMUNE SYSTEM TO CNS

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The study of brain reaction to antigen in norm and pathology as well as afferent pathways of this information creates the ground of development of new kind of treatment

Method

The quantity of cells containing C-Fos protein- marker of cells activation was investigated
- CNS

Results

Application of different kinds of antigens courses the activation of neurons and algorithms of it is different. EAE leads to disorder of this reactions in particular the reactions of orexin-containing neurons.

Bone marrow ,thymus and spleen are connected with the brain by sympathetic afferent nervous fabers . Signals of LPS i.p.injection reach the brain by nervous vagus , vagotomy excludes brain reaction to LPS (L.E.Goehler a.al. 2000; KJ.Ttracy a.al. 2002 and oth.)

Conclusion

The knowledge about afferent pathways is important for clinical use, because this kind of transmission may be increased or reduced pharmacologically

Complex of this results stresses the necessity to understand, what kind of information comes to the brain ach the brain by nervous vagus , vagotomy excludes brain reaction to LPS (L.E.Goehler a.al. 2000; KJ.Ttracy a.al. 2002 and oth.)

AUTO1-0467
NEURONAL AUTOIMMUNE DISEASES

AUTOANTIBODY PROFILING OF AMYOTROPHIC LATERAL SCLEROSIS PLASMA

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Background

Amyotrophic lateral sclerosis (ALS) is the most common neurodegenerative disease in adults that results in muscular paralysis, followed by death within 3-5 years after onset. The aetiology of ALS is not known, which explains the lack of effective treatments. Genetic factors have been found to increase susceptibility to the disease, while autoimmune mechanisms remain somewhat unexplored.

Other neurological disorders, such as Multiple Sclerosis, have known autoimmune components and the relevance of investigating these in ALS is becoming larger. Evidence from biochemical-, morphological-, pharmacological- and physiological studies suggest the existence of such components. However, evidence from larger proteomic studies is lacking. By using a proteomic approach, the aim of our study is to investigate the occurrence of autoantibodies in human plasma samples from ALS patients.

Method

Plasma samples from 233 patients and 204 healthy controls were profiled in this study. Initially, an untargeted screening on a high density planar protein array, containing 42.000 protein fragments representing over 19.000 proteins, was done. This was followed by a targeted multiplexed bead based suspension array, with 352 protein fragments immobilized on magnetic beads.

Results

Profiling of antibody reactivities in all samples enabled identification of differences in reactivity between ALS and control samples. Among others, Glial Fibrillary Acidic Protein (GFAP) and SEC14 Like Lipid Binding 5 (SEC14L5) were identified as potentially interesting targets with higher number of reactive ALS samples compared to controls.

Conclusion

With this study, we wish to increase the knowledge of this unexplored area, and hopefully contribute to further understanding the aetiology of ALS.

AUTO1-0045
NEURONAL AUTOIMMUNE DISEASES

A LARGE SCREEN FOR PARANEOPLASTIC AUTOANTIBODIES; DIAGNOSIS AND PREDICTIVE VALUES

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Background

Paraneoplastic neurological syndromes (PNS) are a group of syndromes that affect the central and peripheral neuromuscular system in association with cancer. Patients are roughly classified into those with "classical" PNS with a strong association with cancer and those with non-classical PNS and less cancer association. Specific antibodies may assist in the diagnosis of PNS. We aim to characterize patients with unexplained neuropsychiatric symptoms, in whom positive PNS antibodies were detected in Sheba medical center, a large referral hospital.

Method

Clinical and demographic data of patients with positive PNS antibodies were collected during the years 2002-2016. Antibodies were tested by either immunoblot analysis (HuD, Yo, RI, CV2, amphiphysin, Ma1, Ma2) or by indirect immunofluorescence test (NMDA, AMPA, LGI1, CASPR2, GABAR).

Results

During the follow up of 14 years, 4010 PNS tests were performed in patients with unexplained neuropsychiatric symptoms. Seventy-two were found to be positive; among them we had full data access to 45. The most frequent antibodies were anti-Hu (31.3%), anti-Yo (17.8%), anti-CV2 (13.3%), and anti-NMDA (8.9%), and the most common cancers were small-cell lung (SCLC) and ovarian cancers. In the "classical" group, cancer was diagnosed in 54.4% of patients, and in the non-classical group, 40.0% were diagnosed with cancer. There was a positive correlation between high antibody titers and the presence of cancer.

Conclusion

PNS panel testing as well as the titer of the antibodies can be helpful in diagnosing malignancy in a selected group of patients.

AUTO1-0093
NEW AVENUES IN SYSTEMIC SCLEROSIS

SAFETY AND EFFICACY OF INTRAVENOUS VERSUS ORAL CYCLOPHOSPHAMIDE (CYC) IN THE TREATMENT OF SYSTEMIC SCLEROSIS (SSC) RELATED ILD AND SKIN INVOLVEMENT

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Background

Po CYC has shown modest effect on SSc-ILD. However, several centres prefer IV monthly CYC mainly because of expected milder toxicity. Our aim was to compare efficacy and safety of po vs iv CYC for SSc.

Method

Data from the EUSTAR database and the Scleroderma Lung Studies I and II on SSc patients, receiving po or iv CYC for at least 6 months, followed for 1 year from last administration, were analysed for safety and efficacy at end of treatment and after one-year follow-up.

Results

148 patients received po CYC and 165 patients received iv CYC. Despite significantly different baseline FVC% and DLCO%, unadjusted %changes in FVC%, DLCO% and mRSS were similar between groups both at end of treatment and follow-up visits (table 1).

	po CYC	iv CYC	*p*
population	142	165	NA
age	48±11	52±12	0.011
treatment duration (days)	365 (1)	335 (321)	0.006
dosage	160(42)/daily	1000(400)/monthly	NA
history of CS treatment	42 (28.4%)	75(45.5%)	0.001
history of DMARD treatme	35(23.6%)	67 (40.6%)	0.001
past/current smoking	21(14.2%)	11(6.7%)	0.022
BL dosage CS	2.7±4.1	5.0±4.4	<0.001
BL FVC% predicted	69 (15)	82(28)	<0.001
END ΔFVC% change	0 (10)	0 (14)	NS
FU ΔFVC% change	0 (13)	-2 (14)	NS
BL DLCO%	51 (24)	56 (29)	0.016
END ΔDLCO% change	-4 (12)	-3 (13)	NS
FU ΔDLCO% change	-3 (13)	-4 (18)	NS
BL mRSS	13 (5)	12 (6)	0.606
END ΔmRSS change	-2 (5)	-1 (6)	NS
FU ΔmRSS change	-2 (7)	-2 (6)	NS
END DMARD use	12 (8.1%)	51 (30.9%)	<0.001
END CS dosage	2.3±3.3	5.4±4.1	<0.001
FU DMARD use	34 (23%)	121 (73.3%)	<0.001
FU CS dosage	2.0±3.4	4.5±4.4	<0.001

Data presented as mean±SD or median(IQR) or prevalence(%)
NA: not applicable, NS: not significant; FVC: fprced vital capacity; DLCO: diffusion of carbon monoxyde; mRSS: modified Rodnan skin score; CS: corticosteroid; DMARDs: disease modifying ant-rheumatic drugs; SAE: serious adverse event; Aes: adverse events; END: end of treatment visit; FU: end of follow-up visit

During po CYC, there was more leukopenia, thrombocytopenia, haemorrhagic cystitis and general AEs; in the iv group, there were more SAEs, need for oxygen and SSc-

related cardiomyopathy during follow-up (Table 2).

	po CYC	iv CYC	*p*
END oxygen supply	4 (2.7%)	12 (7.3%)	NS
END platelet <100.000x10^9/mmc	5 (3.4%)	0 (0%)	0.023
END WBC <2.0x10^9/mmc	32 (21.6%)	2 (1.2%)	<0.001
END haemorrhagic cystitis	8 (5.4%)	0 (0%)	0.006
END total SAEs	21 (14.2%)	22 (13.3%)	NS
END total AEs	74 (50%)	26 (15.8%)	<0.001
FU oxygen supply	7 (4.7%)	24 (14.5%)	0.005
FU cardiomyopathy	3 (2.0%)	14 (8.5%)	0.001
FU total SAEs	12 (8.1%)	28 (17.0%)	0.029
FU total AEs	31 (20.9%)	36 (21.9%)	NS

Data presented as mean±SD or median(IQR) or prevalence(%)
NS: not significant; WBC: white blood cell count; SAE: serious adverse event; Aes: adverse events; END: end of treatment visit; FU: end of follow-up visit

There was also a statistically significant higher dosage of steroids and higher prevalence of DMARDs use in the iv CYC group, as a post-treatment maintenance (table 1).

Conclusion

Despite being somewhat disparate groups, in particular for the different nature of the source databases, preliminary analyses indicates that one year of po and iv CYC had similar results, although dosage of concomitant steroid was lower and subsequent immune-suppressors were less common in the po group. In contrast, AE time courses and types of AEs were different comparing po and iv CYC.

AUTO1-0739
NEW AVENUES IN SYSTEMIC SCLEROSIS

EFFICACY AND SAFETY OF RITUXIMAB FOR SYSTEMIC SCLEROSIS: FRENCH RETROSPECTIVE STUDY AND LITERATURE REVIEW

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Background

We aimed to determine the long term efficacy and safety of rituximab in SSc, determine the factors associated with treatment response and done literature review with pooled analysis of RTX treated patients.

Method

All patients fulfilled the ACR/EULAR criteria for SSc which had received rituximab were included in the study.

Results

thirteen patients which received rituximab were included with age 44 years (16-61 years). MRSS decreased from 13 [5; 26] at baseline to 10 [4; 18] at M12 (p = 0.5), was stabilized in 8 patients and improved in 4 cases. FVC was stable at 72% [62; 85] at baseline to 85% [64;90] at M12 (p = 0.6), and DLCO was stable at 40% [37;54] to 49 [30; 55] at M12 (p = 0.9). In 7 patients with diffuse SSc, mRSS significantly decreased from 29 [22 ; 35] at baseline to 18 [10;19] at M12 (p = 0.06).

Pooled analysis of 53 patients (40 literature and 13 fpersonal series) showed significant improvement of mRSS from 18 [8 ; 32] at baseline to 9 [4;18] at M6 (p = 0.007) and 13 [8;18] at M12 (p = 0.008) and 10 [4;16] at the last follow up (p = 0.0002). FVC improved from 71% [66 ; 80] at baseline to 84% [75;90] at M12 (p = 0.001). DLCO improved from 58% [39 ; 65] at M0 to 63% [53;78% at M12 (p = 0.04).

Conclusion

. Our results suggest efficiency of rituximab in cutaneous and pulmonary involvements, especially in patients with diffuse systemic sclerosis.

AUTO1-0693
NEW AVENUES IN SYSTEMIC SCLEROSIS

LONG TERM STUDY BY SKIN HIGH FREQUENCY ULTRASOUND IN SYSTEMIC SCLEROSIS PATIENTS TREATED WITH ENDOTHELIN RECEPTOR ANTAGONIST

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Background

Systemic sclerosis (SSc) is an autoimmune disorder characterized by skin involvement, which may be recognized by modified Rodnan skin score (mRSS) and skin high frequency ultrasound (US) (1). Endothelin-1 (ET-1) seems implicated in the development of dermal fibrosis (2,3). Bosentan, a dual ET-1 receptor antagonist, seems effective in reducing skin fibrosis in SSc patients (3). The aim of this study was to evaluate long-term effects of bosentan on dermal thickness (DT) in SSc patients.

Method

At baseline (T0), were enrolled 19 patients already receiving cyclic intravenous infusion of iloprost (5 continuous days, average 80 mcg/day, every three months), continued the treatment for further 4 years (ILO group) and 19 patients, although they continued the same cyclic intravenous iloprost treatment as the previous group, also received bosentan 125 mg twice a day for 4 years (ILO+BOS group), due to digital ulcers. DT was yearly evaluated by both mRSS and US (18 MHz probe, MyLab 25, Esaote, Italy) at the level of the usual seventeen skin areas (1-3).

Results

A statistically significant decrease of DT-US was observed in the ILO+BOS group from T0 to T4 ($p=0.01$), no statistical significant variation of mRSS was observed ($p=0.70$). In ILO group, a statistically significant increase of DT-US ($p<0.0001$) and mRSS ($p<0.0001$), was observed.

Conclusion

In this study, long-term treatment with ET-1 receptor antagonist in combination with iloprost seems to decrease DT in SSc patients.

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AUTO1-0856
NEW AVENUES IN SYSTEMIC SCLEROSIS

MORFOLOGICAL AND FUNCTIONAL ASSESSMENT OF MICROVASCULAR INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Background

Systemic Sclerosis (SSc) is an autoimmune connective tissue disease, characterized by structural and functional alterations of microcirculation, with important clinical implications, such as Raynaud Phenomenon (RP) and digital ulcers (1,2).

Method

Morphological and functional assessment of the peripheral microvascular damage is important for diagnosis, prognosis and therapy in SSc patients (2).

Results

Nailfold videocapillaroscopy (NVC) is the best safe, non-invasive and validated method to detect morphological microvascular abnormalities. NVC allows to distinguish secondary RP from both primary RP and healthy subjects, to identify morphological patterns of microvascular damage ('Early', 'Active' and 'Late' patterns) and to calculate the microangiopathy evolution score (MES) to follow disease evolution (3,4). However, capillary blood flow/perfusion cannot be quantitatively measured by NVC in standard conditions, as only a qualitative evaluation may be performed (5).The assessment of cutaneous blood perfusion in SSc may be performed by different laser techniques and by thermografy (6,7).

Conclusion

The evaluation of microvascular structure by NVC, in combination with functional study by laser techniques or thermal imaging, not only can help to distinguish between primary RP to secondary RP, but also to evaluate the response to therapy, and the disease progression.

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AUTO1-0376
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

AUTOANTIBODIES TARGETING FICOLIN-2 AND FICOLIN-3 IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH ACTIVE NEPHRITIS

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Background

Systemic lupus erythematosus (SLE) is a multi-system inflammatory disease characterized by production of various autoantibodies. Lupus nephritis (LN) is one of the most frequent and serious complications in SLE patients. Conventional biomarkers still lack sensitivity and specificity for detecting ongoing disease activity in lupus kidneys and early relapse of nephritis. Although the mechanisms of induction of autoantibodies are not fully deciphered, complement proteins involved in the uptake of dying cells could play a role in the SLE physiopathology. This study aimed to investigate the presence of anti-ficolin-2 and anti-ficolin-3 antibodies in SLE patients and to evaluate their interest in LN.

Method

This retrospective study included 165 SLE patients with low and high disease activity, depending on SLEDAI score. Among them, 38 patients had active LN, documented by kidney biopsy. Anti-ficolin-2, anti-ficolin-3 and anti-C1q antibodies levels were measured in sera by ELISA.

Results

Anti-ficolin-2 and anti-ficolin-3 antibodies were detected as positive respectively in 37% and 35% of SLE patients. The titer of these antibodies was correlated with the SLEDAI score. Only active lupus nephritis was significantly associated with the presence of anti-ficolin-2 or anti-ficolin-3 antibodies (p=0.0001). Interestingly, patients with active proliferative LN showed significantly more positive anti-ficolins antibodies than those with non-proliferative LN. Moreover, the combination of anti-ficolin-2, anti-ficolin-3 and anti-C1q demonstrated higher specificity (98%) than any other traditional biomarker for the diagnosis of active LN.

Conclusion

Our results support the usefulness of anti-ficolin-2 and anti-ficolin-3 as complementary serological biomarkers for the diagnosis of active lupus with renal manifestation.

AUTO1-0775
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

PROTEOMIC PROFILING REVEALS SIX PROTEIN CANDIDATE AUTOANTIGENS ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

In Systemic lupus erythematosus (SLE) there are typically many autoantibodies. The disease heterogeneity could be better understood with discovery of phenotype-specific antigens targeted by autoantibodies. We here aimed to identify novel autoantigens potentially related to SLE-disease and a major complication, atherosclerosis.

Method

Antigen microarrays were used to profile IgG autoantibody reactivity against 77 protein fragments (20-140 amino acids (aa) long, median of 89 aa) produced within the Human Protein Atlas project, in serum samples from SLE patients (n=107) and age- and sex-matched population-based controls (n=107). Common carotid intima-media thickness (IMT), plaque occurrence and echogenicity were determined by B-mode ultrasound.

Results

We determined significant differences between patients and controls in IgG reactivity against 6 proteins. In patients compared to controls, there was an increase of IgG reactivity against zinc finger protein 688 (ZFN688), kinesin family member 15 (KIF15), early B cell factor 2 (EBF2), Crystallin, alpha B (CRYAB) and tumor necrosis factor receptor superfamily member 13C (TNFSF13C). In contrast IgG reactivity against siah E3 ubiquinin protein ligase 2 (SIAH2) was lower among SLE patients.

Of these six affinity proteomics, only antiZFN688 was associated with carotid atherosclerosis (plaque occurrence) and vulnerable plaques in SLE. There was a weak association between anti-EBF2 and SLE disease activity but no significant associations were determined for other measured IgG reactivity.

Conclusion

In this discovery screening we here demonstrate new candidate autoantigens with differential reactivity (reflecting autoantibody levels) in SLE patients and in controls and in relation to atherosclerosis in SLE.

AUTO1-0019
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

PREVALENCE OF ANTI-DFS70 ANTIBODIES IN PATIENTS WITH AND WITHOUT SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

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Background

Autoantibodies to the dense fine speckled 70 (DFS70) antigen are common among antinuclear antibodies (ANA) positive healthy individuals (HI). We assessed the prevalence of anti-DFS70 antibodies in patients with and without ANA-associated rheumatic diseases (AARDs) by two methods: chemiluminescent immunoassay (CIA) and an indirect immunofluorescence (IIF) assay based on immunoadsorption for DFS70.

Method

Fifty-one ANA-positive sera samples from patients with confirmed clinical diagnosis of AARD, 92 samples from HI and 85 samples submitted to a reference laboratory for routine ANA testing were evaluated for the presence of anti-DFS70 antibodies. The samples were evaluated by QUANTA Flash DFS70 CIA using BIO-FLASH instrument and by NOVA Lite selected HEp-2 kit on NOVA View - an automated IIF system. Sera with DFS positive pattern were pre-absorbed with highly purified human DFS70 antigen, and then tested again.

Results

Twenty-four samples (10.5%) tested by QUANTA Flash DFS70 CIA were positive for anti-DFS70 antibodies. The prevalence of monospecific anti-DFS70 antibodies was significantly higher in healthy subjects than in patients with AARDs (10.9% vs. 1.9%, p=0.02). The frequency of anti-DFS70 antibodies in samples submitted for routine ANA testing was 15.2%. A very good agreement was found between CIA and the DFS pattern identified by the automated HEp-2 IIF (kappa=0.97). In 80% of the samples obtained from patients without AARDs, immunoadsorption effectively inhibited the anti-DFS70 antibodies

Conclusion

The data confirm that mono-specific anti-DFS70 antibodies are a strong discriminator between ANA positive HI and AARD patients, and their evaluation should be included in ANA testing algorithms.

AUTO1-0072
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

ANTI-DFS70 AUTOANTIBODIES IN UCTD SUBJECTS: WHAT'S ON THE HORIZON?

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Background

To date there are few serological markers able to predict the evolution of undifferentiated connective tissue diseases (UCTD) into defined connective tissue diseases (CTD). The presence of antinuclear antibodies (ANA) may suggest a CTD diagnosis but may also lead to a diagnosis of UCTD when clinical and serological manifestations are not sufficient to diagnose a defined CTD.

Method

Immunological and clinical records of 91 long-standing UCTD patients were studied. Dense fine speckled (DFS) pattern was determined using the Indirect Immunofluorescence (IIF) ANA test on HEp-2 cells and anti-DFS70 antibodies were tested by chemiluminescence assay (CIA) and then confirmed by DFS70 Immunoblot.

Results

Thirteen (14.3%) of 91 serum samples were positive for anti-DFS70 antibodies by CIA and 2 out of the 13 patients (15.4%) showed monospecific anti-DFS70 antibodies. There was no statistical significance between the prevalence of anti-ENA and anti-DNA autoantibodies in patients with and without anti-DFS70 antibodies. No differences were found in the clinical characteristics of both groups. The presence of the anti-DFS70 antibodies was related to the younger age class.

Conclusion

The high prevalence of the anti-DFS70 antibodies in the UCTD patients suggested the potential role of these autoantibodies as a marker in the evolution of UCTD to CTD.

AUTO1-0652
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

CLINICAL PHENOTYPE OF PATIENTS WHO ARE POSITIVE FOR ANTI-ARS BY ELISA BUT NEGATIVE BY RNA-IMMUNOPRECIPITATION - ANTI-SYNTHETASE SYNDROME OR MIMICKER? -

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Background

Anti-aminoacyl-tRNA synthetase (ARS) antibodies are associated with common clinical characteristics called anti-synthetase syndrome (ASS). After the enzyme-linked immunosorbent assay (ELISA) for anti-ARS have been utilized, we sometimes encounter patients that are positive for anti-ARS by ELISA but negative by RNA-immunoprecipitation (RNA-IP). We analyzed the clinical significance of these cases.

Method

We examined medical records of patients who visited to our department from 2014 to 2017. In 1628 samples, we found 134 samples (78 cases) to be positive for anti-ARSs by ELISA (MESACUP^{TM} anti-ARS test, MBL, Japan) which were subsequently analyzed by RNA-IP. Some parts of the samples were further analyzed by individual antigen-specific ELISA.

Results

Seventeen patients were found to show discrepant results. Compared the previously reported frequency of each ASS characteristics (Love LA. et al. Medicine (Baltimore), 1991), ILD was found in 15 (88% vs. 89%), myositis in 5 (29% vs. 84%, $p<0.01$), polyarthritis in 6 (35% vs. 94%, $p<0.01$), Raynaud's phenomenon in 5 (29% vs. 62%, $p<0.05$), mechanic's hands in 2 (12% vs. 71%, $p<0.01$) and fever in none (0% vs. 87%, $p<0.01$). Specific ELISA showed all samples reacted with one or several ARS recombinant antigens, of which Jo-1 was the most frequently recognized.

Conclusion

Anti-ARSs which are detected in ELISA but not in RNA-IP showed significant association with ILD but not with the other characteristics of ASS, suggesting importance of RNA-IP in diagnosing ASS, although, these antibodies actually recognize recombinant ARS antigens. Further investigation on mechanism of discrepancy between different detection systems is needed.

AUTO1-0215
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

THE IMPORTANCE OF BEING ANTI-DFS70 ANTIBODIES

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Background

In 2016 about 24 000 samples have been screened for ANA at the Laboratorio Unico Metropolitano (LUM) in Bologna.

The discrimination between dense fine speckled pattern (DFS70) and rheumatic disease associated patterns is a challenge for routine diagnostic laboratories and underlines the value of a better understanding of anti-DFS70 antibodies.

Method

From October 2016 to May 2017 we selected 52 samples from our routine on HEp2 Euroimmun cells with a suspicion of DFS70 (38 females and 14 males, range 10-86 years).

For anti-DFS70 antibodies screening four different methods were performed: indirect immunofluorescence (IIF), lineblot (LB) and chemiluminescence assay (CLIA).

Results

Only 2 sera showed discordant results between LB and CLIA, indicating a high level of agreement for these methods. Among all samples, 31/52 (60%) were confirmed positive for anti-DFS70 by CLIA and LB. Therefore our data show that a suspicion for DFS70 pattern in the ANA screening, may not be confirmed after performing CLIA/LB. Subsequently, these second-level method must be used in these patients.

Furthermore, since mono-specific anti-DFS70 antibodies are significantly high in healthy subjects and in patients without AARDs, in order to assess the presence of other autoantibodies, ENA-based methods should be performed in these samples. In fact, mixed patterns of DFS70 and other clinically relevant patterns can be identified.

Conclusion

The benefits of this evaluation should be considered for a DFS70-based ANA testing algorithm.

AUTO1-0254
NOVEL AUTOANTIBODIES IN AUTOIMMUNE RHEUMATIC DISEASES AND ANTI DSF70

AUTOANTIBODIES TO 26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 4 (PSMD4) AND PROTEIN S100-B (S100B) IN SCI PATIENTS

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Background

Recent evidence supports the role of antibody responses as important damaging factors in spinal cord injury (SCI)-induced neuroinflammation. However, since only a limited number of autoantibody targets have been identified, the discovery of novel targets with pathologic and clinical relevance can help to understand the role of autoantibodies in SCI etiology. Using a phage display approach, we recently identified PSMD4 and S100B as autoantibody targets in SCI patients. In the current study, we aimed to further characterize these autoantibodies in SCI patients.

Method

Peptide ELISA were developed to screen for antibody reactivity in a SCI patient cohort (n=175, containing follow-up samples of traumatic and pathologic SCI patients post-injury/surgery), healthy controls (n=94) and patients with distinct pathologies (stroke (n=27), multiple sclerosis (MS, n=54) and rheumatoid arthritis (RA, n=57)).

Results

Using our peptide ELISA, similar PSMD4 and S100B immunoreactivity was found within healthy controls (PSMD4 4% and S100B 5%) and SCI patients (PSMD4 4% and S100B 6%), irrespective of the cause of pathology or time post-injury. Analysis of PSMD4 and S100B immunoreactivity in follow-up samples from the SCI cohort showed that these autoantibodies were already present in the acute phase after SCI and remained stable throughout the follow-up period. Screening of stroke, MS and RA patients demonstrated that PSMD4 and S100B autoantibodies were also not induced by other neuroinflammatory or autoimmune conditions.

Conclusion

Altogether, PSMD4 and S100B autoantibodies are not induced by SCI. Still, since their targets are expressed in the spinal cord, these autoantibodies might contribute to degenerative or recovery processes after SCI.

AUTO1-0136
PATHOGENETIC ASPECTS OF TYPE I DIABETES MELLITUS

IDENTIFICATION OF GAD65 AA 114-122 REACTIVE 'MEMORY-LIKE' NK CELLS IN NEWLY DIAGNOSED TYPE 1 DIABETIC PATIENTS BY HLA-CLASS I PENTAMERS

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Background

Type 1 diabetes (T1D) is an autoimmune disease where pancreatic β cells are destroyed by autoreactive T cells in genetically predisposed individuals. In the disease pathogenesis, several immunotypes unfold important roles i.e. autoreactive $CD4^+$ and $CD8^+$ T cells, autoantibodies producing-B lymphocytes and innate immunity components. In recent years, MHC multimer technology allowed the detection of rare antigen-specific autoreactive T cells in order to unravel their pathogenetic significance.

Method

PBMC from newly diagnosed T1D patients were short-term cultured in the presence of GAD65 114-122 peptide and subsequently stained with HLA A*02:01 GAD65 114-122 pentamers to confirm specific detection in Flow cytometric analysis of increased percentages of GAD65 autoreactive T cells as well as to discover peculiar antigen-reactive immunotypes in respect to healthy controls.

Results

As part of an extended analysis of PBMC of newly diagnosed T1D patients, we provide evidence that GAD65 114-122 pentamers can depict a GAD65 114-122 peptide expandable population of functionally, phenotypically skewed, preliminary characterized $CD3^-CD8^{dull}CD56^+$'memory-like' NK cells. Data suggest that the NK cell subset could bind the HLA class I GAD65 114-122 pentamer through ILT2 inhibitory receptor. In a preliminary attempt to functionally characterize $CD3^-CD8^{dull}CD56^+$ NK cells, CD107a expression revealed increased degranulation in GAD65 114-122 and FLU peptide expanded T1D PBMC following GAD65 114-122 peptide HLA A*02:01 presentation in respect to the unpulsed condition. CD107a expression was enriched in ILT2 positive NK cells.

Conclusion

The pathogenetic significance of the observed $CD3^-CD8^{dull}CD56^+$ $ILT2^+$ 'memory-like NK cell subset' with increased response upon secondary challenge in diabetics remains to be elucidated.

AUTO1-0873
PATHOGENETIC ASPECTS OF TYPE I DIABETES MELLITUS

MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF)-1 AND MIF-2 AN EMERGING FAMILY OF CYTOKINE WITH A PATHOGENETIC ROLE IN IMMUNOINFLAMMATORY AND AUTOIMMUNE DISEASES

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Macrophage migration inhibitory factor (MIF) is a cytokine with pleiotropic actions involved in the pathogenesis of several inflammatory and autoimmune disorders. MIF is constitutively expressed and stored in intracellular pools. It binds to the cell-surface receptor CD74 and to the intracellular receptor, JAB1, as well as to the noncognate receptors, CXCR2 and CXCR4. Recently, a new member of the MIF superfamily has been identified, the D-dopachrome tautomerase (D-DT), which shares structural and functional homology with MIF. We have investigated the role of MIF in the etiopathogenesis of Type 1 Diabetes (T1D) and Multiple Sclerosis (MS). In both spontaneous and accelerated animal models of T1D, high MIF expression was found in splenic lymphocytes. Immunoneutralization of MIF with monoclonal antibodies prevents cyclophosphamide-induced diabetes in NOD mice. Also, neutralization of endogenous MIF with polyclonal antibodies or the small-molecule ISO-1, that inhibits the tautomerasic activity of MIF and abrogates its biological activities, or its genetic deletion, prevents development of immunoinflammatory diabetes induced in mice by multiple low doses of streptozotocin. We have also investigated the expression levels of MIF, its homologue D-DT, and the receptors CD74, CD44, CXCR2 and CXCR4 in encephalitogenic T cells from a mouse model of MS, as well as in circulating T helper cells from MS patients. We show a significant upregulation of the receptors involved in MIF signaling transduction both in the animal model and in patients. Accordingly, higher levels of CD74 in PBMCs from MS patients seem to predispose to earlier clinical relapses. Along the same lines, a significant increase in MIF receptors is found in the CNS lesions associated to MS. Finally, the MIF inhibitor, ISO-1, was shown to reduce TNF-alpha production and antigen-specific proliferation of EAE splenocytes. Overall, this increasing body of data suggests that selective targeting of MIF with either anti-MIF antibodies or specific chemical MIF inhibitors might offer a new therapeutic avenue for autoimmune disorders such as T1D and MS.

AUTO1-0443
PATHOGENETIC ASPECTS OF TYPE I DIABETES MELLITUS

PERIPHERAL LYMPHOCYTE SUBPOPULATIONS AT ONSET OF TYPE 1 DIABETES: IMBALANCE OF NAÏVE AND MEMORY T CELLS

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Background

Type 1 diabetes (T1D) is an autoimmune disorder characterized by destruction of pancreatic beta cells resulting in insulin dependency. Changes in T and B cell subpopulations in peripheral blood of T1D patients have been described, but a comprehensive multiparametric flow cytometric analysis is still lacking.
The aim of this study is to identify changes in peripheral blood T- and B- cell compartments in patients at onset of T1D.

Method

CD4+ and CD8+ T cells (naïve, central memory, effector memory and terminally differentiated effector (TEMRA), Th17 and Tregs) and B cells subsets (naïve, unswitched memory, switched memory and transitional B cells) were analyzed in peripheral blood of T1D patients at onset (n=26) and healthy donors (HD; n=40) using multiparametric flow cytometry.

Results

A decrease in the percentage of early and late effector memory CD4+ and CD8+ T cells (T CD4+: $p=0.001$ and $p<0.001$, T CD8+: $p=0.046$ and $p<0.001$), TEMRA CD4+ and CD8+ cells ($p=0.003$ and $p=0.004$) was found.
In contrast, the percentage of naïve CD4+ T cells ($p=0.010$), and percentage and absolute counts of naïve CD8+ T cells ($p<0.001$ and $p=0.001$) were increased in T1D patients compared with HD.
Moreover, an increase in percentage of total B cells and a decrease of transitional B cells was observed in patients compared with HD ($p=0.015$ and $p=0.006$, respectively).
No changes were found either in Tregs or in Th17 subpopulations.

Conclusion

The observed changes in the percentage and/or absolute number of lymphocyte subpopulations support that effector cells migrate to the pancreas participating in the autoimmune response.

AUTO1-0860
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 1

OVERCOMING SERONEGATIVE DISEASE WITH NEW LABORATORY TOOLS: IMMUNOPRECIPITATION FOR THE DISCOVERY AND VALIDATION OF NEW AUTOANTIBODIES

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Background.
The diagnosis of connective tissue diseases such as systemic sclerosis (SSc) and poly/dermatomyositis (PM/DM) is largely bases on the presence of specific autoantibodies (autoAbs) to be used in the routine clinical practice, as well as rare specificities only sought in research settings (1). On the other hand, seronegative conditions such as psoriatic arthritis (PsA) are burdened by long diagnostic delays largely due to the lack of serum autoAbs. A significant unmet need is that no commercial assay can identify rare autoAbs in connective tissue diseases (2) or new autoreactivities in seronegative conditions. Immunoprecipitation (IP) of protein and/or RNA components of target autoantigens is the gold standard method for the discovery of new and rare autoAbs but is performed only in a few academic laboratories worldwide (3,4). As a result, alternative techniques (i.e. ELISA, immunoblotting) are often preferred for large-scale testing, despite the lack of standardization (5).
Materials and methods.
We have analyzed sera from 300 patients affected by “seronegative” rheumatic conditions (autoAb-negative SSc and PM/DM cases, seronegative PsA) and matched controls without an autoimmune disease and seronegative for anti-nuclear (ANA), anti-ENA, anti-dsDNA, and antiphospholipid antibodies. We performed a first screening on autoAbs through the use of protein- and RNA- IP on serum samples as described in established protocols (6, 7) and after the identification of specific protein and/or RNA bands suggestive for new or rare autoAbs we validated the results by the use of additional techniques (indirect immunofluorescence, ELISA, western blot, and IP-western blot) (6, 7). This approach has been established by the proponent since 2009 and led to the identification of rare autoAbs (i.e. anti-MDA5, -MJ/NXP-2, -mitochondrial antigens, -Th/To, -Ago2/Su) in “seronegative” rheumatic patients.
Expected results.
Our IP approach is a unique opportunity to screen for rare and previously undescribed serum autoantibodies to be implemented in clinical practice.
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AUTO1-0820
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 1

EXTRACELLULAR HISTIDYL-TRNA SYNTHETASE IN MYOSITIS WITH INTERSTITIAL LUNG DISEASE

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Background: Histidyl-transfer RNA synthetase (HisRS) is a major autoantigen in myositis with lung involvement. We investigated the presence of HisRS in the extracellular compartments sera and bronchoalveolar lavage fluid (BAL). In addition, the occurrence of anti-HisRS antibody isotypes was evaluated in BAL and sera from myositis patients.

Methods:

HisRS antigen expression was evaluated by dot-blot in: 1) sera from 38 myositis (18 anti-HisRS positive (+); 20 anti-HisRS negative (-)), 15 rheumatoid arthritis (RA) and 7 sarcoidosis patients, and 22 healthy controls (HC); 2) BAL from 8 myositis (5 anti-HisRS+; 3 anti-HisRS-) and 8 sarcoidosis patients, and 8 HC. In order to confirm dot-blot results, western-blot (WB) was performed on a representative number of individuals from myositis (n=8), sarcoidosis (n=3), and HC (n=3) groups. The presence of anti-HisRS antibody isotypes was evaluated in myositis and healthy BAL and sera by ELISA and addressable laser bead immunoassay.

Results:

Extracellular HisRS antigen was detected by dot-blot in sera from myositis, RA, and HC groups. However, HisRS antigen was found in a higher number of myositis patients (24 of 38 myositis sera, specifically 12 of 18 anti-HisRS(+) and 12 of 20 anti-HisRS(-) sera) in comparison to RA (3/15), sarcoidosis (0/7) and HC (5/22). In BAL analysed by dot-blot, HisRS antigen was detected in 4 of 8 myositis (2 anti-HisRS(+) and 2 anti-HisRS(-)), 6 of 8 HC and 5 of 8 sarcoidosis individuals. WB confirmed the presence of HisRS antigen in BAL from myositis, sarcoidosis and HC. Blocking experiments (the commercial antibody used to detect extracellular HisRS was pre-incubated with recombinant HisRS antigen) were performed by dot-blot to confirm the presence of extracellular HisRS antigen in BAL. A strong black signal was observed in the myositis BAL whereas no signal could be detected in sarcoidosis and HC BAL. The presence of this unknown factor with high binding capacity for HisRS and HisRS complexed with anti-HisRS-N-terminal antibody was not identified as C1q-immune complexes. Surprisingly, anti-HisRS antibody isotypes were detected in myositis BAL: 1) Anti-HisRS IgG were found in 5 of 8 myositis BAL; and 2) Anti-HisRS IgA and anti-HisRS IgM were identified in 3 of 8 myositis BAL. All patients with anti-HisRS isotypes in BAL were anti-HisRS IgG seropositive and diagnosed with interstitial lung disease.

Conclusion:

The HisRS antigen was detected in extracellular compartments, namely sera and BAL, of myositis, sarcoidosis, RA and HC. An unknown binding factor was identified exclusively in myositis BAL, and may be attributed to the presence of local selective autoantibody reactivities. The identification of extracellular HisRS and anti-HisRS antibody isotypes in myositis BAL may suggest local production of autoantibodies and may provide additional clues for the development of autoimmunity in the myositis lung.

AUTO1-0830
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 1

ASPECTS OF SALIVARY GLAND SONOGRAPHY IN SJÖGREN´S SYNDROME

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Background:
The role of sonography in the evaluation of salivary gland alterations in patients with suspected Sjögren´s Syndrome (SjS) and its benefit with regard to the diagnosis is part of continuing investigation. With most studies concentrating on the contribution to the diagnosis, only few reports exist on longitudinal changes in the sonomorphology of salivary glands in patients with SjS. Studies have shown that systemic and local therapeutic interventions are able to influence the results of different sonographic modalities. Despite intense research, many questions in ultrasound of salivary glands remain unanswered. Amongst other things it is unclear why not all patients with SjS manifest sonographic abnormalities, when during the course of SjS sonographic changes occur or if theses sonographic observations proceed the clinical symptomatic. The aim of the presented investigation is the examination of sonographic salivary gland alterations during the five-year follow up of patients with SjS.

Methods:
Patients with SjS diagnosed according to the AECG classification criteria were included in this study. The ESSPRI was applied for the evaluation of patient´s symptoms and the ESSDAI for systemic features. During 2011 and 2016 the sonoelastographic alterations of the salivary glands in patients with SjS were evaluated. Acoustic Radiation Force Impulse (ARFI) imaging (=shear wave velocity), Real Time Tissue Elastography (RTTE) and Virtual Touch Tissue Imaging (VTTI) were applied in addition to B-Mode sonography (BMUS). Results of BMUS, RTTE and VTTI were graded with appropriate scoring systems.

Results:
Fifty patients diagnosed with SjS were included (45 females, age: 56 years). In 2011, the mean ESSPRI score was 8.3 (SD = 4.6) and the mean ESSDAI score was 5.6 (SD = 7.5). Initially, the sonographic evaluation of the parotid gland (PG) resulted in a mean score of 1.6 (SD = 0.6) and in the submandibular gland (SMG) of 1.7 (SD = 1.0), the mean ARFI value of PG was 2.99m/s (SD = 0.93) and the mean ARFI value of the SMG was 2.15m/s (SD = 0.57).
Clinical examination and sonoelastographic evaluation was repeated after five years in 2016, revealing a mean ESSPRI score of 6.1 (SD = 3.2, $p = 0.002$) and a mean ESSDAI score of 4.6 (SD = 7.0, $p < 0.001$). The mean sonographic score of the PG was 1.4 (SD = 0.7, $p < 0.001$) and of the SMG was 1.9 (SD = 1.0, $p = 0.034$). There was a decline in the sonographic score of the PG of 0.27 (SD = 0.5) and increase of the SMG of 0.1 (SD 1.1) on average. After five years a significant decline of ARFI values could be observed in the PG (2.33m/s, SD = 0.70, $p < 0.001$) while no significant changes of the ARFI of the SMG could be observed. Results of RTTE and VTTI did not change significantly. The mean time interval between onset of first symptoms and first sonographic examination in 2011 was 57.3 months (SD = 60.8).

Conclusion:
The five-year sonoelastographic follow up of salivary gland alterations in patients with SjS revealed a decline in the severity of sonographic alterations of the parotid gland in BMUS and ARFI imaging, indicating a certain capability for modulation of salivary gland affection in SjS.

AUTO1-0927
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 1

TYPE I INTERFERON DYSREGULATION IN HUMAN BRAIN DISEASE

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Background

The Type I interferon system is essential to protect the brain against viral infection. However aberrant activation of the type I interferon response is associated with autoimmunity and brain disease. Monogenic neuroinflammatory diseases such as Aicardi-Goutieres' Syndrome are characterised by aberrant activation of the type I interferon response with severe associated brain disease - and show significant genetic and phenotypic overlap with systemic lupus erythematosus. My research has focussed on understanding the cellular and molecular pathways involved in type I interferon-mediated brain damage, showing that these proteins can damage small blood vessels in human and transgenic mouse models of interferon over-expression. I show how ultra sensitive biomarkers such as single molecule ELISA can be used to detect subfemtomolar concentrations of type I interferon proteins, revealing new roles for these cytokines in human inflammatory disease.

Method

Results

Conclusion

AUTO1-0707
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 1

DOMINANT PROTECTION FROM HLA-MEDIATED AUTOIMMUNE DISEASE IS CONFERRED BY ANTIGEN SPECIFIC REGULATORY T CELLS (2nd Prize Winner)

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HLA genes confer susceptibility to, or protection from, autoimmune diseases. However, it has not been clear how these genes effect this increased risk of disease or protection. In this study, we used the model autoimmune disease, Goodpasture's disease, to elucidate a mechanism.
Goodpasture's disease is a disease with a defined target autoantigen, the non-collagenous domain of Type IV collagen; clear diagnostic criteria, including linear deposition of IgG along the glomerular basement membrane; and, has a strong positive association with HLA-DRB1*15:01 (DR15) and a dominant negative association with HLA-DRB1*01:01 (DR1). We compared the crystal structures of DR15 and DR1 presenting the Goodpasture's T cell epitope, α3135-145, and found that the epitope adopted a more pronounced conformation with a flipped backbone in DR1. These changes in peptide-HLA conformation led to alterations in the epitope specific $\alpha\beta$ TCR usage and T cell phenotypes. In both humans and HLA transgenic mice, DR15-α3135-145 specific T cells exhibited a pro-inflammatory Foxp3 negative conventional T cell phenotype and caused disease. In contrast, DR1-α3135-145 specific T cells were predominantly anti-inflammatory Foxp3 positive regulatory T cells (Tregs). Furthermore, in HLA transgenic mice expressing both DR15 and DR1, protection from disease was Treg dependent.
These results demonstrate that positive HLA associations with autoimmune disease can be ascribed to the interaction between HLA and epitopes with antigen specific pro-inflammatory T cells, whereas HLA protection is conferred by the interaction with antigen specific Tregs.

AUTO1-0869
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 1

ROLE OF IMAGING IN LARGE VESSEL VASCULITIS

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Large vessel vasculitis (LVV) is defined as a vasculitis affecting large arteries - namely aorta and its major branches - whose giant cell arteritis (GCA) and Takayasu's arteritis (TAK) represent the two main forms, mainly differentiated by age at onset (>50 years in GCA and <40 years in TAK)1.
The increasing availability and improvement of different imaging techniques are deeply influencing diagnostic approach and follow-up of patients affected with LVV2. Color duplex ultrasonography (CDUS), computed tomography angiography (CTA), magnetic resonance imaging angiography (MRA), and 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) - especially when integrated with CT - , are taking hold as useful techniques to examine aorta and other large vessels in LVV. Imaging is also emerging as a potential outcome measure to evaluate response to treatment, although distinction between inflammatory activity and vascular remodelling during follow-up remains challenging3. Additionally, standardization and validation of some technical parameters are still not available and represent matter of intense study.
The aim of the lecture is to provide current evidence on the role of imaging in LVV, its potential clinical impact on the diagnosis, evaluation of disease extent and management.

References

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AUTO1-0039
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 2

IMAGING MODALITIES FOR THE DIAGNOSIS AND DISEASE ACTIVITY ASSESSMENT OF TAKAYASU'S ARTERITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background

Early diagnosis of Takayasu's Arteritis (TAK) and detection of disease activity may reduce the risk of vascular complications. The objective of this study was to determine the effectiveness of imaging modalities for the management of TAK.

Method

MEDLINE and EMBASE were searched for studies of patients undergoing various imaging modalities for TAK diagnosis or to assess disease activity. We excluded case reports, reviews and case series with < 10 patients. The methodologic quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). Random effects meta-analyses with inverse-variance weighting were performed.

Results

From the 1126 citations screened, 57 studies met our inclusion criteria. Many of the studies were of small sample size (average N=27), cross-sectional design and low methodological quality. Ultrasound (US) had a lower pooled sensitivity (SN) of 81% (95% CI: 69-89%) than magnetic resonance angiography (MRA) with SN= 92% (95% CI: 88-95%) for TAK diagnosis (by clinical criteria and/or X-Ray angiography). Both had high specificities (SP) of >90% for TAK diagnosis. Fewer studies investigated computed tomography angiography (CTA), but SN and SP for TAK diagnosis was high (>90%). The utility of vessel wall thickening and enhancement by MRA and CTA to predict disease activity varied across studies. The pooled SN and SP of ^{18}F-fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) for disease activity was 81% (95% CI: 69-89%) and 74 % (95% CI: 55-86%), respectively.

Conclusion

US, CTA and/or MRA are effective for the diagnosis of TAK. The utility of these imaging modalities for assessing disease activity remains unclear.

AUTO1-0868
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 2

INNATE IMMUNITY AND AUTOIMMUNITY IN MYASTHENIA GRAVIS THYMUS: A PATHOGENIC CROSS-TALK

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Pathogen infections and dysregulated Toll-like receptor (TLR)-mediated innate immune responses are suspected to play a critical role in the development of autoimmune conditions. Considerable evidence supports thymic involvement in myasthenia gravis (MG), a B cell-mediated autoimmune disease affecting neuromuscular junction. Growing data from our group indicate that chronic inflammation and TLR activation are key pathological features of MG thymus, strongly suggesting that, in the context of a genetic susceptible background, persistent TLR signaling in response to pathogens might contribute to intra-thymic MG pathogenesis. Indeed, we provided evidence of viral presence accompanied by TLR up-regulation in MG thymuses, indicative of a dangerous link between innate immunity and adaptive autoimmunity. In particular, our recent studies revealed a pathogenic cross-talk among Epstein-Barr virus (EBV) and two endosomal TLRs, TLR7 and TLR9, known to promote B-cell dysfunction: EBV persistence and reactivation was found in the lymphoid B-cell component of hyperplastic MG thymuses, in association with TLR7 and TLR9 overexpression and abnormal B-cell proliferation. Our data suggested that EBV-driven TLR7/9 signaling may favor autoimmunity onset or maintenance in MG thymus, via autoreactive B-cell activation and proliferation. Recently, we demonstrated the presence of EBV-positive B-cells in thymomas from MG but not from non-MG patients, thus disclosing a contribution of EBV to B-cell tolerance breakdown also in thymoma-associated MG. Our overall findings promise to have relevant therapeutic implications, since future approaches targeting TLR7/9, or components/regulators of their signaling pathways, could represent effective strategies for treating the autoimmune process in MG and other B cell-mediated autoimmune disorders.

AUTO1-0815
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 2

DEREGULATION OF REGULATORY T CELLS: COULD BE AN ANSWER FOR AUTOIMMUNITY IN VITILIGO PATHOGENESIS

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Vitiligo is a common skin disorder characterized by the acquired loss of constitutional pigmentation manifesting as white macules and patches caused by loss of functional epidermal melanocytes. The exact etiology of vitiligo remains obscure, but autoimmunity has been strongly implicated in the development of disease (Figure 1), especially in generalized vitiligo (GV). Regulatory T (Treg) cells play a key role in maintaining peripheral tolerance in vivo through the active suppression of self-reactive T cell activation and expansion, and dysfunction or deficiency of Tregs may result into autoimmune diseases. The T-cell subsets in vitiligo patients including Tregs were evaluated with reference to their effect on disease onset and progression (Dwivedi et al. 2013). The dramatic increase in CD8+ T-cell number and significant decrease in Tregs number in circulation of GV patients, in addition to significant decrease in FoxP3 expression in the CD4+CD25hi Treg cells, suggest that reduced numbers and impaired function of Tregs fail to control the widespread activation of CD8+ T-cells, which may lead to the destruction of melanocytes in GV. Moreover, the decreased Tregs and CD4+/CD8+ ratio correlate with disease onset and progression in GV patients. Treg cell percentage and counts were significantly decreased in active GV patients compared with stable GV patients. The early age group of patients showed lower levels of Treg cells as compared to the late onset groups. Interestingly, female patients showed significant low expression of FoxP3 in CD4+CD25hi Treg cells as compared to male patients suggesting that females may have increased susceptibility towards autoimmunity. This knowledge further confirms the involvement of cellular immunity in development of GV, which is impaired in these patients and may aid in future development of effective immunotherapy for GV.

Reference:
Dwivedi M, Laddha NC, Arora P, Marfatia YS and Begum R (2013). Decreased regulatory T-Cells and CD4+/CD8+ ratio correlate with disease onset and progression in patients with generalized vitiligo. Pigment Cell Melanoma Res. 26(4):586-591.

AUTO1-0637
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 2

THE INTRODUCTION OF MASS SPECTROMETRY FOR ANTIBODY PROFILING: HOW AND WHY?

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The use of antibodies in healthcare are widespread. Antibodies are used amongst others as disease biomarker, as detection reagents for immunodiagnostics, for in-vivo imaging, and as targeted therapeutic intervention. As such, antibodies have a dramatic impact in the way we diagnose, monitor and treat diseases, including autoimmune disease. Strong developments in antibody biosynthetic technology allow new diagnostic and therapeutic opportunities to emerge. To facilitate implementation, laboratory specialists are often challenged to further improve the methods by which we detect, quantitate and profile antibodies. Mass spectrometry provides a unique platform to address these needs and two such examples will be presented here.

Optimal glycosylation of antibodies is essential in the generation of therapeutic biologics with respect to efficacy, pharmacokinetics and immunogenic properties. We demonstrate that high-resolution glycosylation profiling of intact antibodies is possible using nanoLC-chip-QTOF (Figure). The high-throughput and robust method make this technique ideally suited for quality control of biologics, or to study the clinical importance of antibody glycans in health and disease.

Multiple myeloma (MM) is characterized by the clonal expansion of plasma cells in the bone marrow and the secretion of a monoclonal immunoglobulin also referred to as an M-protein. M-protein diagnostics contributes to diagnose, prognosticate and monitor MM patients. Targeted mass spectrometry approaches are ideally suited for ultra-sensitive measurement of unique antibodies. To measure minimal residual disease in blood of patients with multiple myeloma we developed a targeted mass spectrometry assay to detect M-proteins that is over two orders of magnitude more sensitive than conventional M-protein diagnostics.

AUTO1-0831
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 2

AUTOANTIBODIES AGAINST DsDNA MEASURED WITH NONRADIOACTIVE FARR ASSAY – AN ALTERNATIVE FOR ROUTINE LABS

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Autoantibodies against dsDNA are a highly specific marker for systemic lupus erythematosus (SLE), correlating with disease activity/renal involvement. Measurement has been widely performed with ELISA, IIF with Crithidia luciliae test and Farr assay, with the latter proven to be most specific and, at the same time quantitative, with predictive value for disease activity following SLEDAI/BILAG. In our study, Farr assay showed the highest specificity for SLE (98.8%), while ELISAs gave results with highest sensitivities (1). Recently, many new methods have been proposed (multiplex beads assay, microarrays, even surface plasmon resonance) with no real improvement for diagnostic use. Farr assay is still the “golden standard method” however it uses radioactively-labeled DNA and scintillation fluid with organic solvents to enhance the signal. Therefore many laboratories, avoiding radioavctivity, perform combination of two or more methods to achieve sufficient diagnostic accuracy. Our aim was to modify Farr assay omitting radioactively labeled DNA for wider utility in routine laboratories. We proposed a novel fluorescent measurement of antibody bound DNA (FIA) with intercalating dyes, such as PicoGreen, which is dsDNA specific. FIA follows Farr assay precisely (mixing sera and DNA, incubation, precipitation of proteins with bound DNA using ammonium sulfate), till the final step of measuring, when cyanine dye is added, targeting dsDNA and eliminating detection of ssDNA autoantibodies. We tested the FIA method, in parallel with Farr, in 759 samples and found in both 100% diagnostic specificity, while 53/50 % diagnostic sensitivity was found in a group of 70 non-naïve SLE, respectively. Diagnostic accuracy was 0.781 for FIA method and 0.887 with Farr assay. Intra- and inter-assay variability was comparable for both methods. FIA had higher analytical sensitivity, while analytical accuracy in high and borderline results was comparable for both methods.

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Disclosures: None.

AUTO1-0217
PEARLS IN AUTOIMMUNITY (MAI AWARD CANDIDATES) NO. 2

MIXED CRYOGLOBULINEMIA BEYOND HCV: PERSISTENCE OF EXHAUSTED CLONAL B CELL DESPITE VIRUS ERADICATION

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Background

Hepatitis C virus (HCV) associated mixed cryoglobulinemic (MC) vasculitis commonly regresses after successful antiviral therapy, and the recent direct-acting antivirals (DAA) forecast the cure of this disorder in the large majority of patients. However, some reports have highlighted that MC may persist or relapse after sustained virologic response (SVR). The reason(s) for persisting or relapsing cryoglobulinemic vasculitis in HCV-negative patients are seemingly more than one.

Method

Here we describe five cases with persistence (1 case) or late relapse (4 cases) of cryoglobulinemic vasculitis despite SVR and concomitantly with infection or with the development of solid tumor.

Results

Unlike previous reports on early relapses of MC vasculitis after successful antiviral therapy, our patients had no evidence for lymphoma or for persisting occult HCV infection. In all of our cases relapse or overwhelming disease progression were associated with triggering events, such as infection (3) or the development of a solid tumor (2), which share abundant production of immune complexes (Table 1).

Table 1. Patients'characteristics

Age /sex	MC vasculitis	Cryocrit at diagnosis (%)	Antiviral therapy (weeks)	Persist. or relapse	Year of relapse after HCV clearance	MC vasculitis	Cryocrit at relapse (%)	Concomitant disease
61/F	S/M neuropathy, purpura	44	PAR/OMB /RTV +DAS (12)	persist.	-	severe S/M neuropathy, purpura	24	unresectable non-small cell lung cancer
52/M	S/M neuropathy, purpura, arthralgia	4	SOF/SIM (12)	relapse	1	S neuropathy, nephropathy, purpura	1	flu
69/F	S/M neuropathy, purpura; skin ulcers, nephropathy	3	SOF /LED (24)	relapse	1.5	nephropathy, skin ulcers	10	upper respiratory infection
82/F	S neuropathy, purpura; skin ulcers, nephropathy	7	SOF/SIM (12)	relapse	2.5	purpura	1	infection of unknown etiology
38/F	S neuropathy, purpura	3	PEG-IFN + RIBA (12)	relapse	13	purpura	2	unresectable non-small cell lung cancer

Abbreviations: F, female; M, male; S/M, sensory-motor; SOF/LED, sofosbuvir/ledipasvir; SOF/SIM, sofosvubir/simeprevir; PAR/OMB/RTV +DAS, paritaprevir/ombitasvir/ritonavir + dasabuvir; PEG-IFN + RIBA, pegylated interferon + ribavirin

Conclusion

Type II MC is hallmarked by the expansion of a clone of B cells producing an IgM cross-reactive antibody endowed with both rheumatoid factor and anti-HCV activity. Surprisingly, clonal B cells persist in the circulation of MC patients for at least several months after clearance of HCV and clinical response of MC (Del Padre M. et al. Blood 2017;130:35-8), strongly suggesting that this might be the reason for persistence or relapse of vasculitis. The history of one of our patients suggests that clonal B cells might survive for up to 13 years.

AUTO1-0665
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

ANTI-CD20 MONOCLONAL ANTIBODIES IMMUNO-MONITORING IN PRIMARY MEMBRANOUS NEPHROPATHY TO GUIDE PERSONALIZED TREATMENT

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Background

Monoclonal antibodies (mAbs) as rituximab (RTX) can induce immunogenicity resulting in a loss of efficacy of treatment. We aim to monitor RTX therapy in a cohort treated for primary membranous nephropathy (MN) and to assess whether new humanized and fully-human anti-CD20 mAbs could be a therapeutic alternative.

Method

We measured RTX levels and anti-RTX antibodies at M3 and M6 by ELISA in 22 MN patients treated by RTX 1g D0 and D15. We studied anti-CD20 mAbs B cells cytotoxicity in presence or absence of anti-RTX antibodies. Tested anti-CD20 mAbs were: RTX, ocrelizumab (OCRE), obinutuzumab (OBI) and ofatumumab (OFA).

Results

In our cohort, 23% of patients developed anti-RTX antibodies. Non-responder patients had significantly lower serum RTX concentrations at M3 ($p = 0.0011$), higher anti-PLA2R antibodies titer at M3 ($p = 0.0015$) and M6 ($p = 0.0095$). Non-responders developed more frequently anti-RTX antibodies at M6 ($p = 0.021$) Anti-RTX antibodies were neutralizing in 80% of cases. For two patients, anti-RTX antibodies blocked B-cell cytotoxicity for both OBI, OCRE and OFA whereas anti-CD20 mAb efficacy was not impaired for three patients.

Conclusion

Our study provides new insight into RTX monitoring and anti-drug antibodies screening in primary MN. High residual serum RTX levels at M3 are associated with higher remission rate at M6. Neutralizing anti-RTX antibodies are not rare and their presence at M6 is associated with subsequent MN relapse. Anti-RTX antibodies can neutralize other anti-CD20 mAbs. Further studies are needed to develop personalized therapeutic strategies in primary MN based on drug monitoring and immunogenicity testing.

AUTO1-0472
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

IS HERPES SIMPLEX VIRUS-1 A TRIGGER FOR PRIMARY BILIARY CHOLANGITIS-SPECIFIC ANA AGAINST NUCLEAR BODY PML ANTIGEN

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Background

Nuclear body related PML and sp100 antigens are the most prominent primary biliary cholangitis (PBC)-specific ANAs but why these nuclear autoantigens become targets in PBC remains unclear. Amongst potential viral triggers, herpes simplex virus (HSV1) has been considered the most prominent in view of experimental evidence suggesting that this virus has evolved a strategy that specifically targets PML for degradation.

Aim: We hypothesized that if HSV-1 is responsible for the induction of anti-PML, serological evidence of HSV-1 infection will be tightly linked with the presence of anti-PML; to this extent, we tested for anti-HSV-1 antibodies a well defined cohort of PBC patients with or without anti-PML.**Method**

A total of 66 patients with PBC tested for anti-PML were analysed. Anti-HSV1 antibodies against the gB1, gD1 and gC1 dominant HSV-1 antigens were tested by immunobloting.

Results

Amongst 36 patients originally tested for anti-PML and anti-HSV antibodies, 10 (27.8%) were anti-HSV1/PML double positive, 7 (19.4%) were anti-HSV1pos/PML neg, 2 (5.5%) were anti-HSV1neg/PMLpos and 17 (47.3%) were anti-HSV1/PML double negative. Anti-PML antibody presence was associated with anti-HSV1 antibody seropositivity (p=0.002). All anti-HSV1/PML double positive cases recognized HSV1 gC1 but this reactivity was not PML specific as all but one anti-PML antibody negative/HSV1 positive PBC patients also reacted with gC1.

Conclusion

We document an association of PBC-specific anti-PML antibody reactivity with anti-HSV1 seropositivity in PBC but we failed to find a specific viral antigen which could be the triggering impetus for the loss of tolerance to this nuclear body autoantigen.

AUTO1-0080
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

PREDICTIVE AUTOIMMUNITY USING AUTOANTIBODIES: SCREENING FOR ANTI-NUCLEAR ANTIBODIES

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Background

Early detection of antinuclear antibod- ies (ANA) in asymptomatic subjects is useful to predict autoimmune diseases years before diagnosis. ANA have been determined by indirect immunofluorescence (IIF) using human epithelial type 2 (HEp-2) cells, which is considered the gold standard technique. Multiplex technology (BioPlex ANA Screen) has been introduced for ANA evaluation in recent years. Nevertheless, con- cordance between BioPlex and IIF is low and there is no harmonization between both methods for detection of autoantibodies. This study has aimed to clarify the clin- ical significance of autoantibodies detected by BioPlex ANA Screen in subjects with undiagnosed clinical sus-picion of autoimmune disease and to determine the predictive value of autoantibodies detected by BioPlex ANA Screen.

Method

A 3-year follow-up study was performed of 411 subjects without a clear diagnosis of autoimmune dis- eases in whom autoantibodies were detected by BioPlex ANA Screen that were negative by IIF on HEp-2 cells.

Results

At 3 years of follow-up, 312 (76%) subjects were positive for autoantibodies by IIF and 99 subjects contin- ued to be negative. A diagnosis of autoimmune disease was found in most of the subjects (87%).

Conclusion

BioPlex ANA Screen has greater sensitivity than IIF on HEp-2 cells for autoantibodies detection. Early detection of these antibodies by BioPlex can predict pos- sible development of autoimmune diseases.

AUTO1-0214
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

A FINE BIOINFORMATICAL ANALYSIS OF LYMPHOCYTE DISTRIBUTION PREDICTS THE DIAGNOSIS OF SYSTEMIC AUTOIMMUNE DISEASES

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Background

We investigated 194 individuals with SADs (38 primary Sjögren's syndrome (pSS), 47 rheumatoid arthritis (RA), 46 systemic lupus erythematosus (SLE), 42 systemic sclerosis (SSc) patients) and 53 healthy controls (HCs) to determine whether a fine flow cytometry analysis of T and B cell distribution in whole blood could cluster individuals according to disease diagnosis.

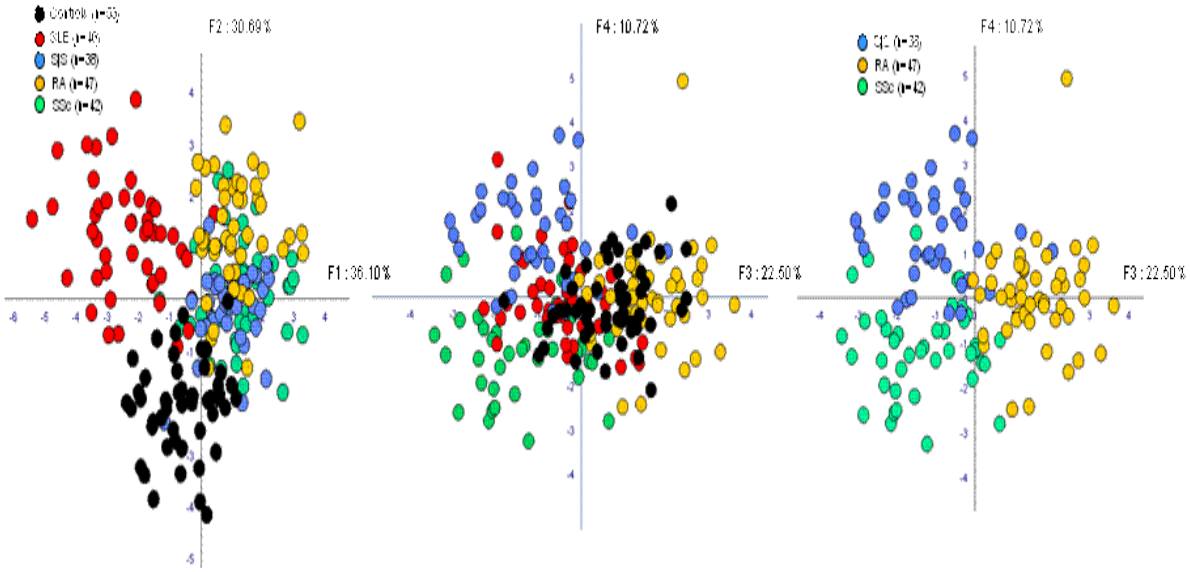
Method

Two flow cytometry panels were designed. A classical manual gating strategy and the Flow-clustering without K (FLOCK) investigation, a density-based clustering approach to algorithmically identify relevant cell populations from multiple samples in an unbiased fashion, were used.

Results

The prediction of the different SADs was determined by discriminant function analysis (DFA). No clustering was found using manual gating. The FLOCK exploration identifies 85 distinct subsets of lymphocytes. The DFA analysis clearly clusters the HCs and the patients according to each SAD (see figure below). When compared to HCs, the pSS signature was discriminated by an increase in $IgD^{hi}CD24^{hi}CD38^{hi}CD27^{-}TACI^{-}CD5^{hi}$ transitional B cells, and an increase of $CD45RA^{+}CD27^{-}CD62L^{lo/-}CD57^{hi}$ effector $CD8^{+}$ T cells. The SLE signature was discriminated by an increase in $IgD^{-}CD24^{lo}CD38^{-}CD27^{-}$

TACI^{+}CD5^{-} memory like B cells, an increase in CD45RA^{-}CD62L^{+}CD38^{hi} activated central memory CD4^{+} T cells. The RA signature was discriminated by an increase in IgD^{hi}CD24^{lo}CD38^{-}CD27^{-}TACI^{+}CD5^{-} unactivated mature naïve B cells. The SSc signature was discriminated by a decrease in CD45RA^{+}CD62L^{+}CD38^{hi} naïve CD8^{+} T cells.



Conclusion

A fine bioinformatical flow cytometry analysis of T and B cell subsets clusterizes patients and HCs suggesting that each SAD can be associated with abnormal specific phenotypical distributions.

AUTO1-0774
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

AUTOIMMUNITY IN THE ELDERLY PATIENT

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Background

Autoimmune diseases vary in manifestation, prognosis and typical age of presentation. Elderly autoimmune patients can be divided in to three main groups. The first subgroup of patients is of "classical" elderly patients presenting with autoimmune diseases associated with old age such as giant cell arteritis. The next group of elderly autoimmune patients include “second peak” patients – with a second peak of disease onset among elderly patient, typically characterized with a milder presentation. Lastly, the third group is a result of the vast medical progress achieved in the past decades, which created a new type of autoimmune patients – elderly patients who survived previously lethal autoimmune conditions. These groups should be considered when treating elderly patients, along with physiologic aging processes effecting the immune system referred as immunosenescence.

Method

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Results

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Conclusion

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AUTO1-0778
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

PREDICTIVE FACTORS OF SEVERE BEHCET'S DISEASE IN A PORTUGUESE COHORT FOLLOWED BETWEEN 1981-2017

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Background

Behçet's disease (BD) is a systemic vasculitis of unkwown cause. The spectrum of the disease ranges from mucocutaneous manifestations to organ disease with relevant morbidity. Associations between disease severity and male sex, earlier age at onset and presence of erythema nodosum are described.

The purpose of this study as to evaluate clinical factors that are associated with manifestations of severe disease.

Method

Retrospective, unicentric cohort study with patients followed in a specialized outpatient clinic between 1981 and 2017. Severe BD cases were defined as presence of ocular, neurological, vascular, cardiac or gastro-intestinal involvement. Statistically significant variables in the univariate model were included in the multivariate model. The adjustment of the multivariate model was evaluated with the Hosmer-Lemeshow test.

Results

Were included 225 patients, of whom 31%are male. Mucous manifestations are present in all patintes, 52% have cutaneous, 40% articular, 27% ocular, 17% vascular, 15% neurological, 5% gastro-intestinal and 0.5% cardiac manifestations; 48% were considered as severe BD. Comparing these patients with non-severe BD cases, we found that severe BD was more frequent in men (OR= 2.00, p=0.019), with increasing age (OR=1.03 per year, p=0.004), in the presence of cutaneous manifestations (OR=2.05, p=0.009), in particular, erythema nodosum (OR=3.02, p=0.001), and in the presence of polyarthritis (OR=4.41, p=0.005). In the multivariate model, age (AOR=1.02, p=0.031), male gender (AOR=2.21, p=0.013), erythema nodosum (AOR= 2.98, p=0.002) and polyarthritis (AOR=4.87, p=0.004) were statistically significant.

Conclusion

Age, male gender, erythema nodosum and polyarthralgias are associated with severe DB forms and therefore should serve as a warning to the clinician.

AUTO1-0017
PRECISIONAL MEDICINE AND PREDICITION OF AUTOIMMUNITY

DECREASE IN 14-3-3 3 ETA PROTEIN LEVELS IS ASSOCIATED WITH DECREASE IN DISEASE ACTIVITY IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS TREATED WITH TOFACITINIB

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Background:

14-3-3η protein is a proinflammatory mediator that may represent a novel diagnostic and prognostic biomarker for rheumatoid arthritis (RA). We assessed disease activity parameters and 14-3-3η protein concentrations in serum of early RA patients treated with Tofacitinib.

Methods:

Paired serum samples from 35 previously non-treated early RA patients (disease onset less than 1 year) receiving Tofacitinib were obtained at baseline and 5 months after the initiation of treatment. Levels of 14-3-3η were measured by JOINT stat 14-3-3η ELISA test kits (Augurex Life Sciences Corp.). The cut-off was defined as 0.19 ng/ml. We investigated the correlation between changes in serum 14-3-3η concentrations and changes in clinical disease activity index (CDAI), simplified disease activity index (SDAI), Disease Activity Score (DAS) 4CRP and DAS4ESR.

Results:

Increased concentrations of 14-3-3η were found in 57% of the patients at baseline and in 37% of the patients after 5 months of treatment. Mean ± SD baseline 14-3-3η concentrations [4.92 ± 8.86 ng/ml] were significantly higher ($p=0.005$) than those found following treatment [1.97 ± 4.59 ng/ml]. Statistically significant improvement ($p <0.001$) of CDAI, SDAI, DAS4ESR and DAS4CRP was achieved after the 5 month of treatment. No correlation was found between absolute 14-3-3η concentrations and parameters of clinical disease activity at both time points. Decrease in 14-3-3η protein levels were highly correlated with improvement in DAS4ESR ($r=0.50$, $p<0.01$) and moderately correlated with improvement in CDAI ($r=0.32$), SDAI ($r=0.33$), and DAS4CRP ($r=0.46$, $p<0.01$).

Conclusion:

The study demonstrates that decrease in 14-3-3η protein concentrations in RA patients treated with Tofacitinib is correlated with improvement of clinical disease activity parameters. 14-3-3η protein is a useful biomarker for monitoring Tofacitinib therapy.

AUTO1-0318
PREGNANCY AND NEWBORNS IN AUTOIMMUNITY

COMBINED EVALUATION OF INNATE AND ADAPTATIVE IMMUNITY TO IDENTIFY RISK FOR EVOLUTION INTO SLE IN WOMEN WITH RECURRENT PREGNANCY LOSS

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Background

In a cohort of women with recurrent pregnacy loss (RPL) we evaluated if an immunological profile was associated with the presence of clinical characteristics observed in autoimmune diseases. In a subset of women with the immunological profile we evaluated the activation status of T-cells.

Method

We evaluated 366 women with RPL and 93 controls. We defined the immune profile as the presence of 2 or more of the following: NK-cell percentages > 15%, positive aPL, positive ANA, positive anti-thyroid antibodies, low complement C3 and low complement C4. Evolution to autoimmune diseases was detected during follow-up. Statistics: Logistic regression.

Results

The prevalence of women with 2 or more immunological abnormalities was 57/366 women (15.6%), significantly higher than in controls. The immunological profile was associated with the following clinical characteristics: Leucopenia (p=0.048), lymphopenia (p=0.007), livedo reticularis (p=0.01), cutaneous rash (p=0.009), and arthritis (p=0.001). During follow-up 17 (4.6%) developed an autoimmune disease that was not present at the time of the diagnose of RPL including SLE and lupus like disease. Women with the immunological profile were at higher risk for evolution into these diseases: OR 4.19, p=0.0055. In 10 women with the immunological profile we observed higher levels of CD8+DR+ T-cells as compared with women without the immune profile.

Conclusion

A subgroup of women with RPL are at risk of developing clinical characteristics of an autoimmune disease. The immunological evaluation of women with RPL might be necessary to identify women that could require a more careful clinical follow-up. Higher CD8+DR+ T-cells might be a pathogenic pathway.

AUTO1-0051
PREGNANCY AND NEWBORNS IN AUTOIMMUNITY

SEROLOGY OF TORCH (TOXOPLASMOSIS, RUBELLA, CYTOMEGALOVIRUS, HERPES VIRUS, PARVOVIRUS-B19, SYPHILIS) IN PREGNANT WOMEN WITH AUTOIMMUNE DISEASES

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Background

The relationship between autoimmune diseases and infections is an interesting and complex issue, and the nonspecific immune activation may lead to false-positive results in serological tests for infective agents.

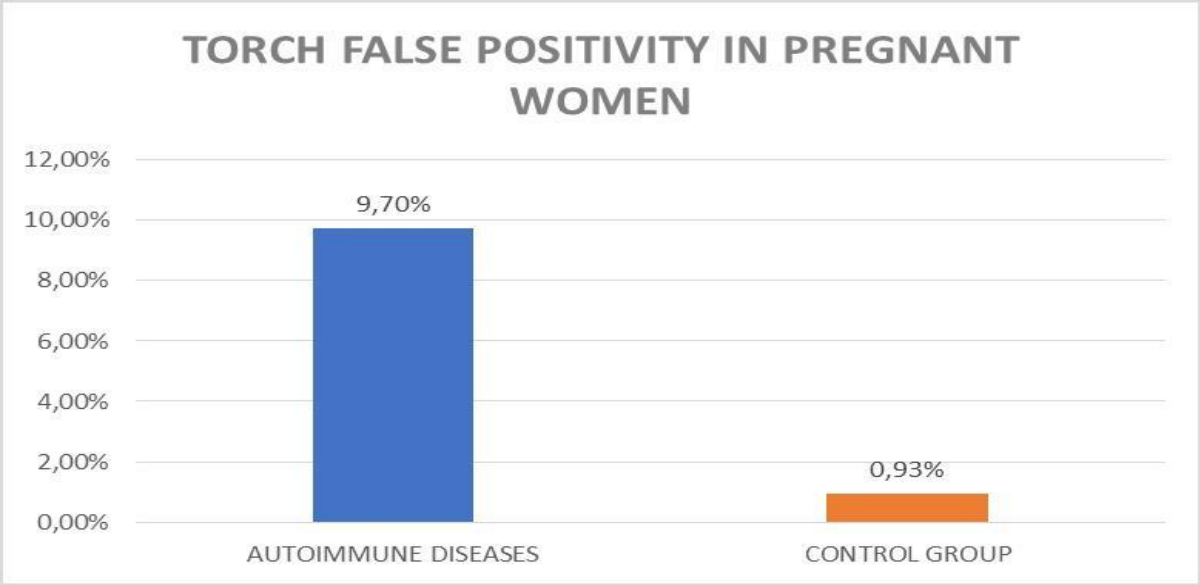
Method

The present study investigated the serology for TORCH infections (IgG and IgM) in women with autoimmune diseases during the pre-conception assessment and/or at the beginning of pregnancy. Data from 145 pregnant women with and autoimmune disease, such as systemic lupus erythematosus (without APS), autoimmune thyroiditis, gastrointestinal autoimmune diseases, arthritis, Sjögren syndrome and connective tissue disease were collected as Study Group. The Control Group consisted of 106 healthy pregnant women.

Results

The rate of positive IgG for Toxoplasmosis and PV B19 resulted higher in the Study Group in comparison with that observed in the Control Group, while there was no major difference between the rates of other infective agents.

Moreover, we analyzed the presence of false-positivity, consisting in the presence of positive TORCH IgM in absence of current infection. In the Study Group a rate of false positivity of 9.70% was found, while in the Control Group it was of 0.93% with a statistically significant difference (OR 10.38, p-value 0.0035).



Conclusion

In our previous studies higher rate of CMV IgM false-positivity in patients with autoimmune diseases was underlined, while in the current study this observation is extended to other infective agents of TORCH. Taking into account that some infections could be a trigger for the onset of autoimmune diseases, the results of the present study can support this hypothesis.

AUTO1-0197
PREGNANCY AND NEWBORNS IN AUTOIMMUNITY

CLINICAL OUTCOME AND PREDICTORS OF MATERNAL AND FETAL COMPLICATIONS IN A PROSPECTIVE COHORT OF 105 SLE PREGNANCIES

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Background

The aim of our study was to assess prognostic factors of maternal/fetal complications in a prospective cohort of SLE pregnant patients.

Method

105 pregnancies in 70 Caucasian SLE-patients were prospectively followed-up. Disease activity was assessed by SLEDAI-2K before conception and after delivery, and by SLEPDAI during pregnancy. We looked at remission in the 6 months before conception and we considered three levels of remission (Zen et al., Ann Rheum Dis, 2015). Pregnancy flares were evaluated by SFI.

Results

At least one maternal or fetal complication occurred in 66/105 pregnancies (62.8%) (**Table 1**). Maternal complications were more common in unremitted patients compared to patients in remission in the 6 months before conception (without any difference among different levels) (90.0 % vs 51.8%, p=0.021). SLEPDAI score at the second and third trimester was significantly higher in patients who had a maternal adverse outcome (p=0.012 and p=0.021, respectively). Fetal complications were significantly associated with anti-dsDNA antibodies at 6 months before conception (64 % vs 35%, p=0.031) **(Table 2).** At the multivariate analysis, we did not find any predictor of maternal complications. Renal flares during pregnancy and positive anti-dsDNA at conception resulted independent risk factors of fetal complications (p=0.026, OR=8.3419 95% C.I.: 1.3-53.7 and p=0.037, OR=4.1327 95% C.I.: 1.1-15.6, respectively), whereas a higher maternal age at conception resulted to be protective (p=0.008, OR 0.7944, 95% C.I.: 0.9-0.7).

Table 1. Maternal and fetal complications in a prospective cohort of 105 pregnancies (70 SLE patients)	
Maternal complications	**N (%)**
Cesarean section	40 (44.4)
Pre-eclampsia	8 (8.4)
Premature rupture of membranes (PROM)	6 (6.3)
Gestational hypertension	3 (3.2)
Gestational diabetes mellitus (GDM)	1 (1.1)
Fetal complications	**N (%)**
Preterm delivery	21 (23.3)
Intrauterine growth restriction (IUGR)	8 (8.9)
Stillbirth	5 (5.1)
Miscarriage	1 (1.0)
Neonatal lupus	1 (1.1)
Atrioventricular block	1 (1.1)

Table 2. Characteristics of 105 pregnancies according to the occurrence of maternal complications or fetal complications (univariate analysis)

Variable	Total	Maternal complications (yes)	Maternal complications (no)	p value	Fetal complications (yes)	Fetal complications (no)	p value
Number	105 (100)	55 (52.4)	50 (47.6)	-	35 (33.3)	70 (66.7)	-
Active disease (yes/no) at conception, n (%)	10 (9.5)	9 (17.0)	1 (2.4)	**0.021**	6 (18.2)	4 (6.7)	**0.088**
Renal flares (yes/no), n (%)	18 (17.1)	12 (22.6)	6 (14.6)	0.328	9 (27.3)	8 (13.6)	**0.104**
Anti-dsDNA at conception (yes/no), n (%)	49 (46.7)	27 (50.9)	22 (52.4)	0.889	22 (66.7)	26 (43.3)	**0.031**
Leucopenia (WBC<3000/mmc) (yes/no), n (%)	6 (5.7)	3 (5.9)	3 (7.7)	0.733	4 (12.1)	2 (3.6)	**0.133**
Lymphopenia (L<1000/mmc) (yes/no), n (%)	17 (17.1)	10 (19.6)	7 (18.4)	0.888	9 (28.1)	8 (14.3)	**0.114**
Low C3 (yes/no), n (%)	46 (43.8)	28 (68.3)	18 (51.4)	**0.134**	18 (66.7)	27 (56.3)	0.377
Low C4 (yes/no), n (%)	11 (10.5)	8 (19.5)	3 (8.6)	**0.153**	6 (22.2)	5 (10.4)	**0.165**
24h proteinuria >0.5g/day (yes/no), n (%)	7 (6.7)	6 (12.5)	1 (3.1)	**0.147**	3 (11.1)	4 (7.7)	0.612
Prednisone (yes/no) at conception, n (%)	43 (40.9)	23 (42.6)	20 (50.0)	0.476	11 (35.5)	30 (50.0)	**0.187**
Azathioprine (yes/no) during pregnancy, n (%)	25 (23.8)	18 (33.3)	7 (16.7)	**0.065**	12 (35.3)	13 (21.7)	**0.151**
Antiplatelet drug (yes/no) during pregnancy, n (%)	59 (56.2)	29 (53.7)	30 (71.4)	**0.077**	21 (61.8)	37 (61.7)	0.993
Mother age at conception (years), mean (SD)	33 (±4.7)	33 (±4.6)	32 (±4.5)	**0.064**	34 (±4.9)	32 (±4.2)	**0.054**
SLEDAI-2k at conception, mean (SD)	1.6 (±1.7)	1.9 (±2.0)	1.2 (±1.2)	**0.126**	1.8 (±1.8)	1.5 (±1.7)	0.261
SLEPDAI 2nd trimester, mean (SD)	1.7 (±2.3)	2.3 (±2.5)	1.1 (±1.9)	**0.012**	2.2 (±2.5)	1.5 (±2.2)	**0.124**
SLEPDAI 3rd trimester, mean (SD)	1.6 (±2.3)	2.0 (±2.3)	1.2 (±2.3)	**0.021**	2.2 (±2.4)	1.4 (±2.2)	**0.090**
Fetal complications (yes/no), n (%)	35 (33.3)	24 (45.3)	10 (24.4)	**0.037**	-	-	-
Maternal complications (yes/no), n (%)	55 (52.4)	-	-	-	24 (70.6)	29 (48.3)	**0.037**

Continuous variables were compared with t-test or Mann-Whitney tests; categorical variables were compared with chi-square or Fisher's exact test as appropriate.
SD: standard deviation; WBC: white blood cells; L: lymhpocytes; n: number; SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000; SLEPDAI: Systemic Lupus Erythematosus Pregnancy Disease Activity Index.

Conclusion

Our study suggests that a worst fetal outcome is predicted by anti-dsDNA antibodies at the time of conception and renal flares during pregnancy.

AUTO1-0747
PREGNANCY AND NEWBORNS IN AUTOIMMUNITY

LONG-TERM SAFETY OF CERTOLIZUMAB PEGOL EXPOSURE FOR THE OFFSPRING OF WOMEN AFFECTED BY RHEUMATOID ARTHRITIS TREATED THROUGHOUT PREGNANCY: IMPLEMENTED CASE SERIES

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Background

Certolizumab pegol (CTZ) is a TNFα inhibitor indicated for RA treatment. High disease during pregnancy is related to poor maternal-fetal outcomes, raising the necessity of achieving the remission at conceiving and during gestation. We aimed to assess the safety of CTZ administration during RA pregnancies.

Method

We prospectively enrolled nine RA women, diagnosed according to 2010 ACR/EULAR criteria, exposed to CTZ throughout the entire course of pregnancy.

Results

All cases were free from any potentially teratogenic drugs, stopped at least 6 months before conceiving. Due to the underlying disease activity, and considering the recent approval for CTZ to be continued throughout the whole pregnancy duration, we carried on with the treatment. Mean maternal age at conception was 31.6±40 months; mean disease duration dated of 51±26 months. Mean gestational duration was 37±3 weeks and mean birth weight 3.037±0.58 grams. Two patients experienced cesarean section, while the others had vaginal delivery. Mean APGAR scores after 1, 5 and 10 minutes were all above 8. No obstetric, perinatal or neonatal complications were observed. Seven newborns out of nine were breastfed. After a 12-months observational gap, the totality of babies was healthy and the development ranges above the 75th percentile. All babies underwent the Italian scheduled vaccine program, without experiencing any complications. Their anticorpal vaccine response is nowadays being investigated by our Research team.

Conclusion

Our data confirm the safety of CTZ administration during pregnancy of RA patients, regarding both the mothers and their offspring. Further large perspective, controlled studies are needed to confirm this statement.

AUTO1-0563
PREGNANCY AND NEWBORNS IN AUTOIMMUNITY

NEWBORN AND MATERNAL THYROID AUTOIMMUNE DISEASE – A THREE YEARS RETROSPECTIVE STUDY

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Background

Thyroid hormones are recognise as esssencial for early brain development. Pregnancy can produce an impact on the thyroid gland and function. Furthermore, 10% to 20% of all pregnant women in the first trimester of pregnancy are thyroid peroxidase (TPO) or thyroglobulin (ATG) antibody positive and euthyroid.
Fetal and neonatal hyperthyroidism are usually produced by transplacental passage thyrotrophin receptor stimulating antibodies (TRAbs). Fetal and/or neonatal hypothyroidism is a rare disorder, its incidence is nearby 1:4000, females are affected about twofold as males.

Method

Thyroid function test of newborns are accomplished during the first two postnatal weeks. Serum TSH, FT4, anti-TPO, and ATG are measured by chemiluminescence assay, and TRAbs is measured by radioimmunoassay.

Results

The aim of this study is to perform a retrospective revision of thyroid function tests in newborn infants and relate them with maternal thyroid disorders.
The vast majority of infants are diagnosed through newborn serum thyroid function tests. If maternal antibody-mediated hypothyroidism is suspected, measurement of maternal and neonatal TRAbs will confirm the diagnosis.

Conclusion

Autoimmune thyroid disease in pregnancy is a very important risk factors both for the mother, fetus and newborn infant.

AUTO1-0170
PREGNANCY AND NEWBORNS IN AUTOIMMUNITY

HYDROXYCHLOROQUINE IN LUPUS PREGNANCY: A META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

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Background

The goal of this individual participant meta-analysis was to pool data from multiple cohorts to determine whether hydroxychloroquine (HCQ) treatment affects pregnancy outcomes.

Method

The literature was searched for prospective cohorts of lupus pregnancies and datasets transferred to Duke University for analysis. HCQ use was defined as use any time during pregnancy. Outcomes of interest included fetal loss, preterm birth, high disease, and preeclampsia. Data from each cohort were collected and analyzed individually. Pooled ORs were calculated in Review Manager. Due to multiple pregnancies per patient, one pregnancy was randomly selected per patient and only included women with first trimester visits.

Results

The current analysis included 611 pregnancies from seven cohorts, 71% exposed to HCQ during pregnancy.

Fetal Loss: Among patients with a history of lupus nephritis, taking HCQ during pregnancy reduced the risk of fetal loss by 76% (OR: 0.24; 95% CI: 0.07-0.83; Table 1).

Preterm Birth: There was no evidence that HCQ decreased the risk of preterm birth.

Disease Activity: HCQ use during pregnancy may reduce the risk of high disease activity during pregnancy among patients with lupus nephritis (OR: 0.47; 95% CI: 0.21-1.09).

Preeclampsia: Among patients with APS, there may be a protective effect of HCQ, but precision of the estimate was limited (OR: 0.55; 95% CI: 0.12-2.45).

Table 1. Pooled odds ratios for the association of hydroxychloroquine use and pregnancy outcomes.

	Fetal Loss	**Preterm Birth**	**High Disease Activity**	**Preeclampsia**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall	**0.50 (0.27, 0.94)**	0.95 (0.58, 1.55)	0.69 (0.35, 1.39)	1.19 (0.62, 2.30)
Lupus Nephritis History	**0.24 (0.07, 0.83)**	0.81 (0.35, 1.89)	0.47 (0.21, 1.09)	0.70 (0.24, 2.03)
No Lupus Nephritis History	0.70 (0.33, 1.46)	1.04 (0.57, 1.89)	0.98 (0.45, 2.17)	1.36 (0.58, 3.16)
APS	0.39 (0.10, 1.47)	0.82 (0.23, 2.96)	1.30 (0.16, 10.48)	0.55 (0.12, 2.45)
No APS	0.61 (0.31, 1.20)	0.96 (0.56, 1.64)	0.70 (0.40, 1.22)	1.28 (0.58, 2.84)
High Disease Activity at 1st Visit	0.61 (0.13, 2.89)	1.53 (0.42, 5.62)	--	0.93 (0.12, 7.14)
No High Disease Activity at 1st Visit	0.46 (0.21, 1.02)	0.81 (0.45, 1.44)	0.73 (0.29, 1.87)	1.07 (0.50, 2.31)

Conclusion

Among patients with lupus nephritis, HCQ use decreased the risk of fetal loss and may decrease high disease activity during pregnancy. The heterogeneity of data collection suggests the need for a unified approach to identify larger cohorts of lupus pregnancies.

AUTO1-1072
PSORIASIS AND PSORIATIC ARTHROSIS

SERUM MATRIX METALLOPROTEINASE-3 NORMALIZATION IS A POTENTIAL PREDICTOR FOR LESS ONE-YEAR RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS

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Background and objectives:
Our previous study showed continuously elevated serum matrix metalloproteinase (MMP)-3 predict radiographic progression in rheumatoid arthritis (RA). Whether serum MMP-3 normalization is a predictor for better outcome remain elusive. Here we explored the association of serum MMP-3 normalization with clinical and radiographic outcome in RA.
Methods:
RA patients with moderate to high disease activity (DAS28-CRP>3.2) were followed up at 1st, 3rd, 6th and 12th months. Serum MMP-3 was detected by ELISA at baseline and each visit. Hand/wrist X-ray at baseline and 12th month were assessed with the Sharp/van der Heijde modified sharp score (mTSS).
Results:
There were 200 RA patients finished one-year follow-up and 58(29%) showed radiographic progression (mTSS≥0.5). RA patients without radiographic progression had significant lower MMP-3 than those with progression at baseline and each visit (Figure 1A, all P<0.001). There were 13.0%, 14.5%, 17.0%, 25.5% and 31.0% patients having normal MMP-3 at baseline and each visit, with significantly lower percentage of these patients showing radiographic progression than those with elevated MMP-3 (Figure 1B, all P<0.05). Among patients with normal CRP at each visit, significantly lower percentage of these patients with normal MMP-3 showed radiographic progression than those with elevated MMP-3 (Figure 1C, all P<0.05). Among patients achieved therapeutic target at each visit, significantly lower percentage of these patients with normal MMP-3 showed radiographic progression than those with elevated MMP-3 (Figure 1D, all P<0.05).

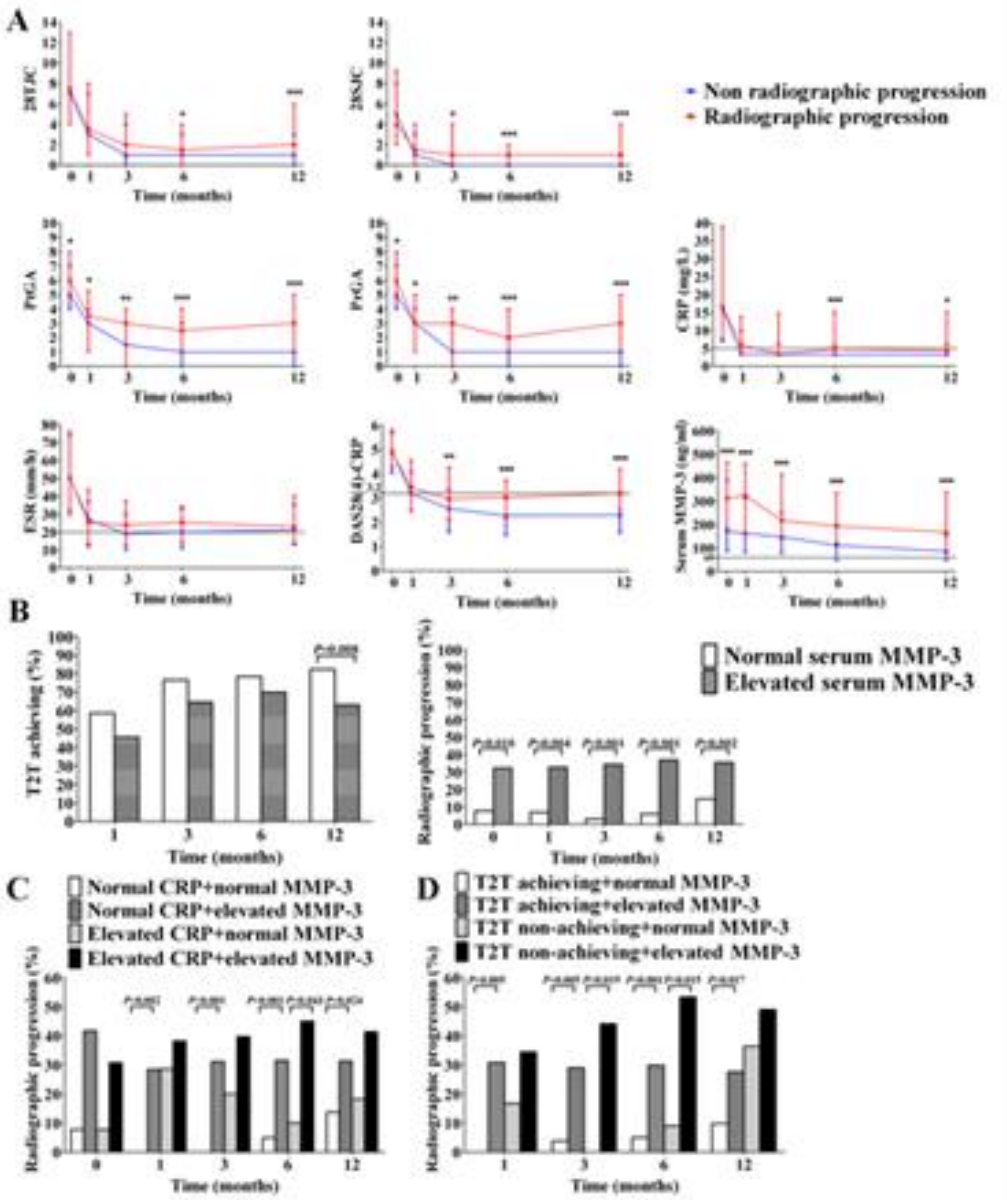

Figure 1 Dynamic change of serum MMP-3 and other indicators in RA patients.
A Comparison of disease activity and radiographic progression indicators between RA patients with and without radiographic progression. **B** Comparison of T2T achieving and the percentage of RA patients showing radiographic progression between normal and elevated serum MMP-3 groups at each visit. **C** Comparison of the percentage of RA patients showing radiographic progression among groups with or without normal CRP and serum MMP-3. **D** Comparison of the percentage of RA patients showing radiographic progression among groups with or without T2T achieving and normal serum MMP-3.

Conclusion:
Serum MMP-3 normalization may be a potential predictor for less one-year radiographic progression in RA.
244w

AUTO1-0032
PSORIASIS AND PSORIATIC ARTHROSIS

RATIONALE OF FRACTION OF EXHALED NITRIC OXIDE (FeNO) MEASUREMENT IN PSORIATIC PATIENTS

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Background

Psoriasis is a chronic auto-inflammatory systemic disease characterized by a wide range of comorbidities. Respiratory comorbidities are currently poorly characterized and with discordant results.

Method

We reviewed Pubmed, Embase, Scopus with these key words differently composed: "airway inflammation", "FeNO", "psoriasis". We selected manually only trials and observational studies in English, Italian and Spanish.

Results

We found 15 records.

Conclusion

The systemic state of inflammation caused by psoriasis acts both de novo on respiratory tissues and also amplifies pre-existent inflammation from asthma or chronic obstructive pulmonary disease. Because the lungs act as a gas exchanger between the internal and external environment, the impact of chronic psoriasis inflammation may be easily assessed through the analysis of exhaled breaths. The fraction of exhaled nitric oxide (FeNO) test is a possible non-invasive solution which can provide a quantitative and qualitative indicator of respiratory airway inflammation. FeNO is routinely used to screen and manage asthmatic patients. Recent pilot studies contain encouraging data that underline its possible use with systemic inflammatory non-pulmonary diseases, such as psoriasis. FeNO may therefore be a useful tool to evaluate underestimated airway inflammation in psoriatic patients.

AUTO1-0928
PSORIASIS AND PSORIATIC ARTHROSIS

CORRELATIONS BETWEEN HLA-Cw6 AND IL-23 IN PSORIASIS VULGARIS

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Background

Psoriasis vulgaris is a common chronic inflammatory proliferative skin disease, and represents a complex disease at cellular, genomic and genetic levels in which HLA-Cw6 is associated with psoriasis susceptibility allele. The pathogenesis of the disease is not yet fully understood, but it is believed to have an autoimmune basis and mediated by Th1 type of lymphocytes. IL-23 induces primary cellular source of pro-inflammatory cytokines which mediate the epidermal hyperplasia, keratinocyte immune activation and tissue inflammation in psoriasis.To determine the role of IL-23 in psoriasis vulgaris, we studied its correlation with HLA-Cw6 in psoriasis vulgaris.

Method

Sixty patients from Dermatology and Venereology Department Outpatients of M. Djamil Hospital were enrolled in cross-sectional study. Blood samples from patients diagnosed with psoriasis vulgaris (n=30) and non-psoriatic patients (n=30) as control group, were tested for plasma level of IL-23 by using ELISA methods, and HLA-CW6 allele by PCR-SSP method.

Results

The results of this study showed that IL-23 levels were significantly higher in patients with psoriasis (31,20±10,58 ng/mL) than in control group (25,58±5,39 ng/mL). The HLA-CW6 allele were found in 20% of psoriasis vulgaris patients while no HLA-Cw6 allele found in control group. The level of IL-23 in psoriatic patients with HLA-Cw6 allele tend to be higher compare to psoriatic patients without HLA-Cw6 allele, although it was no significantly different.

Conclusion

We conclude that our data shown an association between circulating IL-23 and psoriasis vulgaris and indicates that HLA-Cw6 could play a role in occurrence of psoriatic inflammation through IL-23 cytokines.

AUTO1-0153
PSORIASIS AND PSORIATIC ARTHROSIS

ALEXITHYMIA IN INFLAMMATORY ARTHRITIS: PRELIMINARY INVESTIGATION IN A CLINICAL SAMPLE OF PATIENTS AFFECTED BY RHEUMATOID AND PSORIATIC ARTHRITIS

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Background

Rheumatoid arthritis (RA) and Psoriatic arthritis (PsA) are chronic autoimmune disease that lead to an overthrow of articular structure, functional limitation and disability. Alexithymia is a personality trait characterized by deficits in cognitive processing and regulation of emotions. A broad association between alexithymia and symptoms as depression, inflammation, and pain has been demonstrated. Authors proposed that patients affected by inflammatory arthritis can develop alexithymia

Method

We prospectively enrolled, from January to October 2017, patients affected by RA diagnosed according to ACR revised criteria, or PsA diagnosed according to the CASPAR criteria referred to the out-patients clinic of the Rheumatology Unit of Policlinico Tor Vergata, Rome. The 20-item Toronto Alexithymia Scale (TAS-20) was used to assess alexithymia. Disease activity, function and quality of life were assessed. Statistical comparisons were performed using Pearson's Coefficient of Skewness

Results

A total of 20 RA patients and 62 PsA patients were enrolled (Table 1). The TAS-20 score showed that 39% (32/82) patients had alexithymia, 28% (23/82) patients were in the borderline of alexithymia and 33% (27/82) patients did not have alexithymia. A statistical significant association was observed between alexithymia and female gender ($p<0.5$) (Fig.1) and alexithymia and corticosteroid therapy ($p<0.5$) (Fig. 2); no correlations were observed between alexithymia disease duration and therapies.

Conclusion

This study suggests that alexithymia assessment should be a part of the comprehensive care of patients with RA and PsA. We are in the process of extending this investigation on a larger sample population to improve our investigation field to correlation between alexithymia and clinimetrics

AUTO1-0264
PSORIASIS AND PSORIATIC ARTHROSIS

PIGMENTARY CHANGES IN SYSTEMIC SCLEROSIS: A WINDOW TO SEVERITY

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Background

Pigmentary changes though common in systemic sclerosis, are never studied in context of severity.

Method

In this cross-sectional observational study on 50 patients fulfilling the ARA criteria for systemic sclerosis the pigmentary changes were evaluated in context of overall disease severity.

Results

There was a female preponderance (7.33:1). The disease duration was from 9 months to 25 years. 84% patients had received or were receiving various treatment modalities like immunosuppressives. Modified Rodnan Skin Score (MRSS) was 4-46. Pigmentary changes (hyperpigmentation and/or salt-and-pepper pigmentation) were seen in 92% of patients. And had a higher mean MRSS (p value 0.03). A rising trend in the number of patients with hyperpigmentation was found as MRSS increased (p value 0.04). There was a statistically significant correlation between lung involvement as depicted by FVC < 75% and the mean HRCT score (p value < 0.001).

The biopsies from hyperpigmented area showed uniform basilar pigmentation in majority of the cases whereas those from salt-and-pepper pigmentation showed variegation in basilar pigmentation with somewhat alternating in some. Dermal sclerosis was seen in majority of the cases which was more prominent in the lower dermis.

Conclusion

On correlating pigmentary changes with the mean MRSS score, we found that patients with presence of any form of pigmentary changes had a higher mean MRSS score as compared to those without pigmentary changes (p value 0.03). On correlating the MRSS grading with pigmentary changes, a rising trend in the number of patients with hyperpigmentation was found as the severity of MRSS increased (p value 0.04).

AUTO1-0266
PSORIASIS AND PSORIATIC ARTHROSIS

ASSOCIATIONS OF ELEMENTS OF ANTIGEN-PRESENTING MACHINERY WITH PSORIASIS VULGARIS IN POLISH POPULATION

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Background

Psoriasis affects about 2% of Caucasians. The disease is immune-mediated, and is strongly associated with the HLA class I molecule HLA-C*06:02 in most human populations. It seems reasonable to also predict an association of psoriasis with genes coding for molecules of antigen-presenting machinery such as immunoproteasome elements (LMP2 and LMP7) which produce peptides from intracellular proteins, transporter associated with antigen processing (TAP1 and TAP2) which transport these peptides to the endoplasmic reticulum, and endoplasmic reticulum aminopeptidases (ERAP1 and ERAP2) which trim peptides to the optimal length for binding to human leukocyte antigen class I (HLA-I) molecules, which, in turn, present them to CD8+ T lymphocytes on the cell surface.

Method

461 unrelated Polish patients diagnosed with psoriasis vulgaris, and 454 unrelated healthy Polish blood donors were bled and genomic DNA was extracted. Single nucleotide polymorphisms (SNPs) of LMP2, LMP7, TAP1, TAP2, ERAP1, ERAP2 as well as four SNPs in HLA-C specific for HLA-C*06:02 allele were genotyped using the TaqMan SNP Genotyping Assays. Results were analyzed using PLINK software ver. 1.07.

Results

Our preliminary (in the moment of sending this abstract) results seem to suggest a role for ERAP1, ERAP2 and TAP2 polymorphisms in psoriasis, in addition to confirmation of a strong association of HLA-C*06:02 with this disease, particularly with juvenile psoriasis.

Conclusion

ERAP2 and TAP2 polymorphisms appear to be novel risk factors for psoriasis, not published so far.

AUTO1-0911
PSORIASIS AND PSORIATIC ARTHROSIS

REGULATORY MOLECULES AND CELLS IN SKIN OF PSORIATIC PATIENTS.

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Background

Psoriasis is one of the most disabling skin diseases, in which T cells play a major pathogenic role. Skin biopsies taken from psoriasis patients are heavily infiltrated with T cells, mainly pro-inflammatory such as CD4 and TH-17 T cells. These are the source of many pro-inflammatory cytokines, such as IL-12, IL-17 - targets of many therapeutic agents in this field. The status of local regulatory molecules and cells in psoriasis and other immune mediated skin diseases is still lacking. We therefore designed this study aiming to analyze T regulatory cells and other regulatory molecules such as neuropilin-1 (NP-1), semaphorin3A and CTLA4 (marker of T regulatory cells) and also IL-10 and IL-17 in these skin biopsies.

Method

Skin biopsies taken from 20 Psoriasis patients and 5 skin biopsies taken from normal controls were subjected to this study. We used specific antibodies against IL-10, Il-17 for immunohistochemistry and double immunofluorescence for semaphorin3A\CTLA4 and neuropilin-1\CTLA4- as regulatory molecules on T regulatory cells.

Results

The positive staining of semaphorin3A\CTLA4 and neuropilin-1\CTLA4 was significantly higher in normal skin compared to skin biopsies taken from psoriatic patients. In correlation with the above difference, the staining of IL-10 was significantly lower in psoriatic skin compared to normal skin.

Conclusion

Taken together, the above mentioned results point to decreased expression of regulatory molecules in psoriatic skin that may contribute to the inflammatory nature of the disease.

AUTO1-0267
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

MSC-DERIVED EXTRACELLULAR VESICLES: A NOVEL THERAPEUTIC OPTION IN SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis (SSc) is a rare intractable autoimmune disease, with unmet medical need. Cell therapy using mesenchymal stem cells (MSC) is a promising approach, and we recently reported its efficacy in a murine model of SSc induced by hypochlorite (HOCl). Since MSC act primarily through the secretion of soluble factors released within extracellular vesicles (EV), the use of these EV instead of the whole cell preparation seems an attractive alternative. Herein, we compared the effects of two types of EV: exosomes (EX) and microparticles (MP) HOCl-induced SSc.

Method

BALB/c mice were challenged with daily intradermal HOCl injections during 6 weeks to induce SSc. Each group was treated at mid-experiment with infusions of $2.5x10^5$ murine MSC, 250 ng EX or MP isolated from IFNγ-activated or non-activated (NA) MSC. We measured skin thickness every week. At euthanasia (d42), we analyzed the expression of fibrotic and inflammatory markers (collagens 1 and 3, αSma, TGFβ, MMP 1 and 9, TIMP1, IL1β, IL6, TNFα) in lungs and skin samples using RT-qPCR.

Results

Mice treated with EV displayed lower clinical scores, less histological lesions, lower expression of fibrotic and inflammatory markers, with enhanced expression of remodeling parameters in skin and lung tissues. The observed effects were similar to those obtained with MSC. No difference was noted between NA and IFNγ-activated EV.

Conclusion

MSC-derived EV display potent antifibrotic properties in murine SSc. This new acellular therapy represents a promising approach in this disease.

AUTO1-0863
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

ANGINA DUE TO EXTRINSIC COMPRESSION OF THE LEFT MAIN CORONARY ARTERY IN A PATIENT WITH PULMONARY ARTERY HYPERTENSION SECONDARY TO SYSTEMIC LUPUS ERYTHEMATOSUS.

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Background

Systemic lupus erythematosus (SLE) is characterised by the second highest prevalence of pulmonary arterial hypertension (PAH) after systemic sclerosis: 0.5-17.5% depending on the method of diagnosis. We describe the case of a 37-year-old woman with SLE-associated PAH who had been in clinical remission for about nine years.

Method

She at her last visit in May 2017 complained that for some months she had been experiencing episodes of aspecific chest pain sometimes associated with a sense of constriction of the jugular notch mainly during physical activity.

Electrocardiography revealed sinus rhythm with signs of right ventricular overload, and echocardiography showed a dilated and hypokinetic right ventricle unchanged from previous examinations. The result of a walking test was substantially the same as that of previous tests (distance walked 545 metres), and the findings of right cardiac catheterism were unchanged from six months before (RA10 mmHg; PAPm 52 mmHg; PCW 10 mmHg; cardiac output 2.57 L/min; cardiac index 1.66 L/min/m^2; PVR 16.34 mW). Coronary artery CT showed the dilated pulmonary artery compressing and reducing the calibre of the LMCA, and coronary angiography showed an eccentric narrowing of its ostio-proximal portion; there were no atherosclerotic lesions in the coronary tree. Intravascular optical coherence tomography confirmed the diagnosis of an eccentric stenosis of up to 70% indicating external compression.

Results

The patient therefore underwent direct medicated stenting of the LMCA, which led to the complete resolution of her anginal symptoms.

Conclusion

Extrinsic compression of the LMCA is a serious and potentially fatal complication in patients with PAH and angina.

AUTO1-0340
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

TAM RECEPTORS PLASMA CONCENTRATIONS PREDICT PULMONARY ARTERIAL HYPERTENSION IN A COHORT OF SCLERODERMA-RELATED DISORDERS PATIENTS

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Background

The early identification of those Systemic Sclerosis (SSc) patients harbouring Pulmonary Arterial Hypertension (PAH) is a mainstay in the management of SSc. Novel biomarkers might improve the specificity of screening algorithms currently available. In this study we aimed to test the potential diagnostic value of two promising biomarkers, the soluble receptors sMER and sAXL.

Method

We prospectively recruited 80 patients affected by Scleroderma related disorders (Mixed connective tissue disease N. 7, 9%; SSc N. 65, 81%; Scleroderma overlap syndromes N. 8, 10%) in a PAH outpatient clinic of a University Hospital. All patients underwent an extensive and specific PAH screening program based on clinical, laboratory and echocardiographic evaluation. Patients with suspected PAH were addressed to Righ heart catheterization (RHC) to confirm diagnosis.

Results

According to echocardiography and RHC, 12/80 patients were diagnosed with PAH. Table 1 and table 2 show the differences between groups, with respect to echocardiographic findings, lab and clinical data. Patients affected by SSc-related PAH (PAH-SSc) showed a higher sMER and sAXL concentrations (also see Figure 1, panel A). However, the mean Pulmonary Artery Pressure (PAP) measured by right heart catheterization, was directly related to sAXL plasma concentration (ρ= 0.732; p=0.007), but not to sMER plasma concentration (figure 1, panel B).

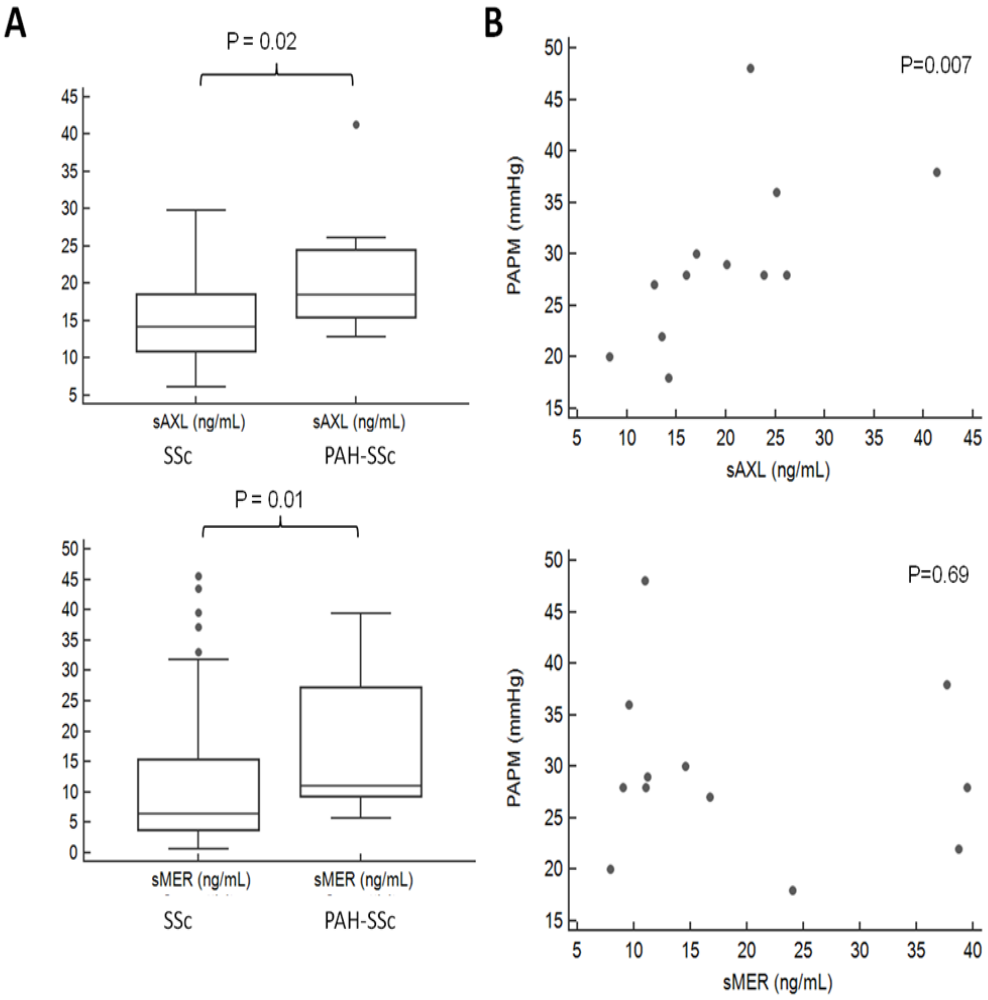
Table 1

	General population (N.=80)	SSc (N.=68)	PAH-SSc (N.= 12)	P
Age, years	67.5 (57.5 - 74.0)	65 (55 - 74)	70 (67 - 77)	0.09
Disease duration, years	7 (3 - 12)	7 (3 - 12)	11 (3 - 12)	0.45
Hemoglobin, g/dL	12.7 (11.4 - 13.8)	12.9 (11.4 - 13.8)	11.9 (11.4 - 12.6)	0.20
WBC (×10⁹/L)	6.5 (5.4-8.1)	6.5 (5.4 - 8.2)	6.6 (5.9 - 7.9)	0.80
PLTs(×10⁹/L)	231 (195 - 286)	237 (202 - 296)	196 (182 - 256)	**0.04**
ESR, mm/h	20 (7 - 33)	20 (7 - 30)	15 (14 - 17)	0.97
CRP, mg/dL	0.20 (0.07 - 0.65)	0.18 (0.85 - 0.46)	0.77 (0.04 - 0.98)	0.34
Creatinin,mg/dL	0.78 (0.69 - 0.96)	0.76 (0.67 - 0.90)	0.95 (0.72 - 1.17)	0.07
Uric acid, mg/dL	4.8 (3.7 - 6.0)	4.7 (3.7 - 5.48)	6.2 (4.8 - 7.6)	**0.02**
BNP, pg/mL	78.1 (36.9 -135.3)	61.4 (34.4 - 113.8)	314.3 (89.6 - 581.7)	**0.0001**
TSH, uUI/mL	2.21 (1.44 - 3.15)	2.20 (1.43 - 2.98)	3.02 (1.56 - 4.04)	0.28
FEV1, %	103 (86 - 114)	103 (85 - 115)	101 (88 - 109)	0.68
FVC, % 9 (85 - 115)		99 (85 - 115)	99 (95 - 113)	0.68
FEV1/FVC, %	109 (102 - 116)	110.5 (103.5 - 117. 0)	102.0 (99.5 - 109.0)	0.05
DLCO-VA, %	89.0 (72.0 - 97.3)	90 (77 - 101)	49 (46 - 70)	**0.0002**
DLCO-HB, %	75.5 (55.5 - 85.5)	76 (64 - 86)	44 (41 - 51)	**0.0003**
EF, %	64.0 (59.2 - 67.0)	65.0 (60.0 - 67.7)	63 (57.0 - 64.5)	0.13
PAP, mmHg	29.0 (25.0 - 34.7)	27 (24 - 33)	53.5 (48 - 73)	**< 0.0001**
TAPSE, mm	23.0 (20.0 - 24.0)	23.0 (20 - 24.5)	20.0 (18.0 - 22.7)	**0.02**
Right atrium Area, cm²	14.0 (11.0 - 18.0)	14 (11 - 16)	19 (18 - 26)	**0.002**
sAXL, ng/mL	15.10 (11.13- 19.32)	14.28 (12.48 - 16.41)	18.53 (15.13 - 24.94)	**0.02**
sMER, ng/mL	7.67 (4.06-15.85)	6.42 (3.87 - 15.27)	11.10 (9.26 - 27.21)	**0.01**

Table 2

	SSc (N= 68)	PAH-SSc (N= 12)	P
Gender (F / M)	62 / 6	11 / 1	0.96
Interstitial Lung Disease (- / +)	43 / 25	4 / 8	0.06
Digit ulcers (- / +)	26 / 42	7 / 5	0.19
Digit ulcers in the last month (- / +)	60 / 8	12/0	0.21
Teleangectasia (- / +)	40 / 28	5 / 7	0.28
ACA (- / +)	36 / 32	4 / 8	0.21
Anti-Scl-70 (- / +)	56 / 12	10 / 2	0.93
Anti-U1-RNP (- / +)	61 / 7	11 / 1	0.84

Figure 1



Conclusion

sAXL and sMER plasma concentration are higher in SSc patients developing PAH; sAXL is a promising biomarker for the early identification of PAH, being directly related to the mean PAP measured by RHC.

AUTO1-0348
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

RED CELL DISTRIBUTION WIDTH IS A PROMISING MARKER OF PULMONARY ARTERIAL HYPERTENSION IN SCLERODERMA-RELATED DISORDERS

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Background

The early identification of those Systemic Sclerosis (SSc) patients harbouring Pulmonary Arterial Hypertension (PAH) is a mainstay in the management of SSc. Novel biomarkers might improve the specificity of screening algorithms currently available. In this study, we aimed to test the diagnostic value of the red cell distribution width coefficient of variation (RDW), already proposed as a putative prognostic marker in thromboembolic and idiopathic PAH.

Method

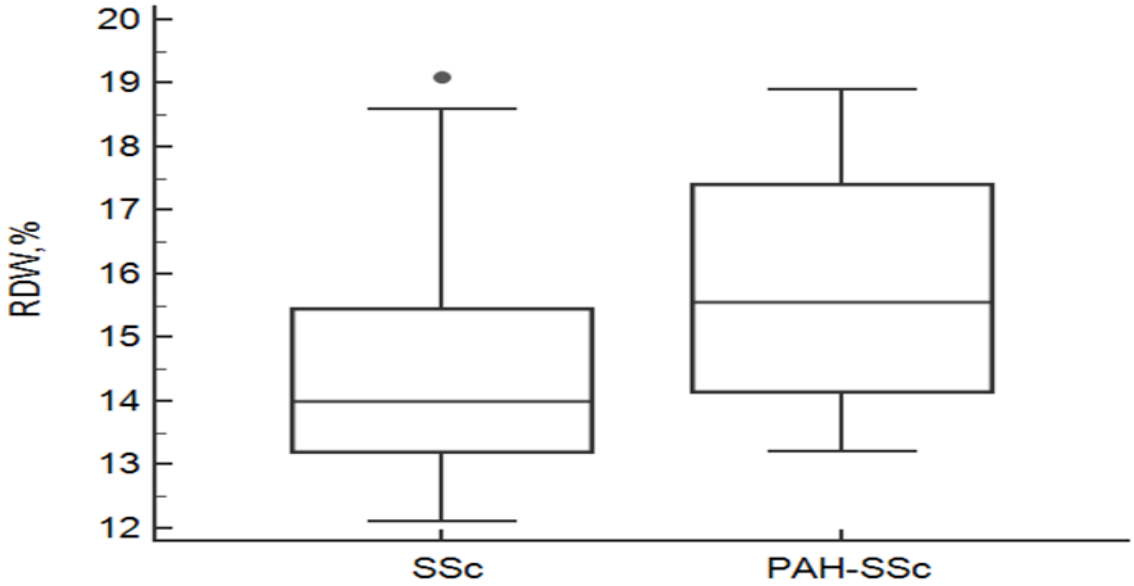
We prospectively recruited 80 patients with Scleroderma related disorders (Mixed connective tissue disease N. 7, 9%; SSc N. 65, 81%; Scleroderma overlap syndromes N. 8,10%) in a PAH outpatient clinic of a University Hospital. All patients underwent an extensive and specifc PAH screening program based on clinical, laboratory and echocardiographic evaluation. Patients with suspected PAH were addressed to right heart catheterization (RHC) to confirm diagnosis.

Results

Based on the echocardiographic screening andthe results of right heart catheterization, 12/80 patients were diagnosed with PAH. Table 1 and table 2 show the differences between groups, with respect to echocardiographic findings, lab and clinical data. Patients affected by PAH had a higher RDW (see Figure 1), which was also directly related to ultrasound-assessed Pulmonary Artery Pressure (PAPs) (ρ= 0.272; p=0.016). Furthermore, among lab values related to PAPs, only RDW (ρ= 0.582; p= 0.047) and BNP (ρ= 0.641; p= 0.024) were independently related to the mean PAP measured by RHC.

	General population (N.=80)	SSc (N.=68)	PAH-SSc (N.= 12)	P
Age, years	67.5 (57.5 - 74.0)	65 (55 - 74)	70 (67 - 77)	0.09
Disease duration, years	7 (3 - 12)	7 (3 - 12)	11 (3 - 12)	0.45
Hemoglobin, g/dL	12.7 (11.4 - 13.8)	12.9 (11.4 - 13.8)	11.9 (11.4 - 12.6)	0.20
RDW, %	14.1 (13.2 - 15.7)	14.0 (13.2 - 15.4)	15.6 (13.2 - 18.9)	**0.01**
WBC ($\times 10^9$/L)	6.5 (5.4-8.1)	6.5 (5.4 - 8.2)	6.6 (5.9 - 7.9)	0.80
PLTs($\times 10^9$/L)	231 (195 - 286)	237 (202 - 296)	196 (182 - 256)	**0.04**
ESR, mm/h	20 (7 - 33)	20 (7 - 30)	15 (14 - 17)	0.97
CRP, mg/dL	0.20 (0.07 - 0.65)	0.18 (0.85 - 0.46)	0.77 (0.04 - 0.98)	0.34
Creatinin,mg/dL	0.78 (0.69 - 0.96)	0.76 (0.67 - 0.90)	0.95 (0.72 - 1.17)	0.07
Uric acid, mg/dL	4.8 (3.7 - 6.0)	4.7 (3.7 - 5.48)	6.2 (4.8 - 7.6)	**0.02**
BNP, pg/mL	78.1 (36.9 -135.3)	61.4 (34.4 - 113.8)	314.3 (89.6 - 581.7)	**0.0001**
TSH, uUI/mL	2.21 (1.44 - 3.15)	2.20 (1.43 - 2.98)	3.02 (1.56 - 4.04)	0.28
FEV1, %	103 (86 - 114)	103 (85 - 115)	101 (88 - 109)	0.68
FVC, % 9 (85'- 115)		99 (85 - 115)	99 (95 - 113)	0.68
FEV1/FVC, %	109 (102 - 116)	110.5 (103.5 - 117. 0)	102.0 (99.5 - 109.0)	0.05
DLCO-VA, %	89.0 (72.0 - 97.3)	90 (77 - 101)	49 (46 - 70)	**0.0002**
DLCO-HB, %	75.5 (55.5 - 85.5)	76 (64 - 86)	44 (41 - 51)	**0.0003**
EF, %	64.0 (59.2 - 67.0)	65.0 (60.0 - 67.7)	63 (57.0 - 64.5)	0.13
PAPs, mmHg	29.0 (25.0 - 34.7)	27 (24 - 33)	53.5 (48 - 73)	**< 0.0001**
TAPSE, mm	23.0 (20.0 - 24.0)	23.0 (20 - 24.5)	20.0 (18.0 - 22.7)	**0.02**
Right atrium Area, cm^2	14.0 (11.0 - 18.0)	14 (11 - 16)	19 (18 - 26)	**0.002**

	SSc (N= 68)	PAH-SSc (N= 12)	P
Gender (F / M)	62 / 6	11 / 1	0.96
Interstitial Lung Disease (- / +)	43 / 25	4 / 8	0.06
Digit ulcers (- / +)	26 / 42	7 / 5	0.19
Digit ulcers in the last month (- / +)	60 / 8	12/0	0.21
Teleangectasia (- / +)	40 / 28	5 / 7	0.28
ACA (- / +)	36 / 32	4 / 8	0.21
Anti-Scl-70 (- / +)	56 / 12	10 / 2	0.93
Anti-U1-RNP (- / +)	61 / 7	11 / 1	0.84



Conclusion

As an inexpensive candidate marker for the detection of SSc-related PAH, RDW is worth to be tested along withcurrent screening algorithms to verify whether their diagnostic performancecould be improved.

AUTO1-0701
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

RHEUMATOLOGICAL ASSESSMENT IS ESSENTIAL TO INTERSTITIAL LUNG DISEASE DIAGNOSIS

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Background

Interstitial lung diseases (ILDs) are a diverse group of parenchymal lung disorders. Currently, a multidisciplinary team (MDT) including pulmonologists, radiologists, and pathologists is the gold standard for ILD diagnosis. Recently, additional subtypes of connective tissue disease -ILD (CTD-ILD) with autoimmune-features (IPAF) were defined; making the rheumatological assessment increasingly important. We aimed to assess the impact of adding routine rheumatology to the MDT.

Method

A prospective study that assessed newly diagnosed ILD patients by two separate blinded arms; all patients were diagnosed by the MDT (e.g. history, physical examination, blood tests, pulmonary function tests and biopsies (if needed)) and by a rheumatologist (e.g. history, physical examination, blood plus serological tests).

Results

Sixty patients were assessed with mean age of 67.3±12 years, 55% male, and 28% smokers. The rheumatological assessment reclassified 21% of the idiopathic pulmonary fibrosis (IPF) as CTD. Moreover, the number of CTD/AIF-ILD increased by 77%. These included ANCA vasculitis, anti-sythetase syndrome, IPAF and IgG4 related ILD. Retrospectively, rheumatological evaluation could have saved seven bronchoscopies and one surgical biopsy.

Conclusion

Adding routine rheumatology assessments to the MDT would significantly increase diagnostic accuracy and reduce invasive procedures.

AUTO1-0227
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

FIBROSIS DEVELOPMENT IN HOCL-INDUCED SYSTEMIC SCLEROSIS: A MULTISTAGE PROCESS HAMPERED BY MESENCHYMAL STEM CELL THERAPY

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Background

Skin fibrosis is the hallmark of systemic sclerosis (SSc) a rare intractable disease with unmet medical need. We previously reported the anti-fibrotic potential of mesenchymal stem cells (MSCs) in a murine model of SSc. This model, based on daily intra-dermal injections of hypochlorite (HOCl) during six weeks, is an inducible model of the disease. In this study, we aimed at characterizing the development of skin fibrosis in HOCl-induced SSc, and evaluating the impact of MSC infusion during the fibrogenesis process.

Method

In a longitudinal study, we decomposed HOCl-SSc induction in three time-periods and examined skin thickness, histological and biological parameters after three weeks (d21) and six weeks (d42) of HOCl challenge, and three weeks after HOCl discontinuation (d63). Treated-mice received intravenous infusion of $2.5x10^5$ MSC three weeks before sacrifice (d0, d21 or d42).

Results

HOCl injections induced a two-step process of fibrosis development: first, an ‘early inflammatory phase’, characterized at d21 by highly proliferative infiltrates of myofibroblasts, T-lymphocytes and macrophages; second, a phase of ‘established matrix fibrosis’, characterized at d42 by less inflammation, but strong collagen deposition. A third phase of ‘spontaneous tissue remodelling’ was observed after HOCl discontinuation, characterized by fibrosis partial receding, due to enhanced MMP1/TIMP1 balance. MSC treatment reduced skin thickness in the three phases of fibrogenesis, exerting more specialized mechanisms: immunosuppression, abrogation of myofibroblast activation, or further enhancing tissue remodelling.

Conclusion

HOCl-SSc mimics three fibrotic phenotypes of scleroderma, all positively impacted by MSC treatment, which demonstrates the great plasticity of MSC, a promising cure for SSc.

AUTO1-0281
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

AMINAPHTONE INCREASES SKIN BLOOD PERFUSION AND IMPROVES RAYNAUD'S PHENOMENON CLINICAL SYMPTOMS, ALSO IN SYSTEMIC SCLEROSIS PATIENTS.

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Background

Aminaphtone is a vasoactive drug recently demonstrated to improve the symptoms of Raynaud's phenomenon (RP) (1). Laser speckle contrast analysis (LASCA) is a validated technique to measure skin blood perfusion (2).
Aim. To evaluate both skin blood perfusion and clinical symptoms related to RP changes during aminaphtone treatment in RP patients, in a six-month observational study.

Method

37 patients with RP were enrolled during routine clinical assessment (27 secondary RP to systemic sclerosis, 10 primary RP). Aminaphtone 75 mg twice daily was administered in addiction to current treatments. Blood perfusion was assessed in all patients by LASCA at baseline (T0), after one (T1), four (T4), twelve (T12) and twenty-four weeks (T24) of treatment, in different areas of hands and face. Raynaud condition score (RCS) and both Raynaud's attack frequency and duration were also assessed at the same times.

Results

A progressive statistically significant increase of blood perfusion was observed from T0 to T24 in all skin areas analyzed. A progressive statistically significant decrease of RCS ($p<0.0001$), Raynaud's frequency ($p=0.03$) and duration ($p=0.0007$) was also recorded from T0 to T24. The results were similar in both primary and secondary RP patients ($p=0.40$). Aminaphtone administration had to be stopped in 2 patients due to headache.

Conclusion

This study demonstrates that aminaphtone treatment increases in short-time skin blood perfusion, as well as improves RP symptoms.

References. 1. Parisi S, et al. Am J Int Med 2015;3;204-9. 2. Ruaro B, et al. Ann Rheum Dis. 2014;73:1181-5.

AUTO1-0834
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

PREDICTORS FOR MORBIDITY AND MORTALITY AT 6 AND 9 YEARS OF FOLLOW-UP IN AN INCEPTION COHORT OF PATIENTS WITH SYSTEMIC SCLEROSIS

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BACKGROUND:
Several studies have investigated the predictors of morbidity and mortality in Systemic sclerosis (SSc). However long-term follow-up data from inception cohorts of early SSc patients are limited.
OBJECTIVES:
To identify predictors of morbidity and mortality in a single centre inception cohort of early SSc patients at long-term follow-up.
METHODS:
Our inception cohort comprised SSc patients who fulfilled the American College of Rheumatology criteria, were recruited within 12 months of disease onset and followed prospectively for at least 3 years. Clinical manifestations, laboratory and lung function tests were recorded at baseline and at 3rd and 6th year of follow up. Multivariate regression analysis and Cox proportional hazard models were used to identify predictors (clinical manifestations, laboratory and lung function tests at baseline) of morbidity and mortality in SSc, respectively.
RESULTS:
A total of 115 patients (97 female, mean age at diagnosis 48.1±13.5 years, 54 diffuse subtype) were recruited, from January 1997 to June 2014. All patients were followed for at least 3 and 84 patients for at least 6 years. Twenty three patients died during a mean follow up of 101.8±48.5 months. In multivariate regression analysis predictors for major SSc outcomes at 6 years were: diffuse subtype (OR: 4.4, p= 0.033), upper gastrointestinal involvement (OR: 4.79, p=0.038) and digital ulcers (OR: 7.9, p= 0.014) at baseline for the development of pulmonary fibrosis (PF). The presence of cardiac rhythm disorders at baseline was a predictor for the development of pulmonary hypertension (PH) (OR=6.05, p=0.022) while older age at disease onset (OR: 1.12, p=0.002) and the presence of antiScl70 (OR= 4.3, p= 0.038) for the presence of rhythm disorders. Cox proportional hazard models analysis revealed 6 factors as independent predictors of mortality: age at disease onset, male gender (HR: 3.63, p=0.025), diffuse type (HR: 2.83, p=0.095), PF (HR: 3.7, p=0.032), PH based on echocardiography (HR=7.49, p=0.008) and DLCO <60% of predicted value (HR: 3.17, p=0.035). Mortality rates at 3 and 6 years were 86% and 76% for patients with 3 factors and 54% and 47% for patients with 4 to 6 factors present at disease onset.
CONCLUSION:
Results from long-term follow-up data from a single centre inception cohort indicate that diffuse SSc subtype, esophageal involvement and digital ulcers at baseline are independent predictors for the development of PF. Male gender, diffuse subtype, PF, PH and decreased DLCO at baseline are independent predictors of mortality.

AUTO1-0123
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

AUTOIMMUNE INTERSTITIAL LUNG DISEASE IN LATIN AMERICA. RESULTS OF THE EPIMAR COHORT STUDY

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Background

Autoimmune interstitial lung diseases (Ai-ILD) represents an specific subgroup of interstitial lung diseases (ILD), of which information about prognosis and natural history is lacking. The objective of this study was to evaluate the characteristics and evolution of patients treated for AI-ILD in Latin-America.

Method

We conducted an ambispective multicenter cohort study in 39 centers of Argentina, Colombia and Uruguay between January 2015 and July 2017. Patients were included if they were diagnosed with AI-ILD by a multidisciplinary team as suggested by current reviews. Patients were classified in the following sub-groups: ILD associated tissue connective disease (ILD-CTD), pneumonia interstitial with autoimmune features (IPAF) and ILD associated an ANCA positive (ILD-ANCA). All images were reviewed by a blinded board certified radiologist.

Results

Of the 185 patients included during the study period, 137 (74%) were women. Median age was 52 years-old. One-hundred and fifty two (87%) patients were classified as ILD-CTD (rheumatoid arthritis 29.8%, systemic sclerosis 25.8%, dermatomyositis 14.5%). Thirteen patients were classified as IPAF and 10 as ILD-ANCA. Mean time between the diagnosis of CTD and manifestation of ILD was 3.3 years. Forty-seven percent of patients showed slight restriction at moment of diagnosis. The most common treatment strategy was the combination of steroids and cyclophosphamide (26.4%) or azathioprine (14.7%).

Conclusion

To the best of our knowledge, this is the first study to evaluate the characteristics and treatment strategies used in patients affected by AI-ILD in Latin-America. Future studies should evaluate the impact of current treatment strategies in the outcome of AI-ILD.

AUTO1-0009
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

IMAGING ASPECTS OF INTERSTITIAL LUNG DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS: LITERATURE REVIEW

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Background

Interstitial lung disease (ILD) is a frequent and severe complication of rheumatoid arthritis (RA), resulting in pulmonary fibrosis and respiratory failure. Chest computed tomography (CT-c) or high resolution CT (HRCT) is the main modality for assessment of ILD.

Method

We performed a systematic literature review on CT-c/HRCT findings in patients with ILD-RA, using the MEDLINE database for the period from 1991 to 2015. We identified records: RA AND ILD AND chest CT OR HRCT - 102; RA AND pulmonary diseases AND chest CT OR HRCT - 216; rheumatoid lung AND chest CT OR HRCT - 144. We removed duplicates and reviewed the records again; records mainly reporting on CT-c or HRCT findings related to ILD-RA and its complications were included into the final analysis (55 articles).

Results

Findings on CT-c/HRCT attributed to ILD-RA are variable (ground glass opacities, reticular and nodular pattern, as well as a combined pattern of emphysema and pulmonary fibrosis). Correlation of CT-c/HRCT findings with clinical data is inconsistent.

Conclusion

ILD-RA is part of a general autoimmune inflammation and should be integrated into the decision-making process for the treatment of RA. There is an unmet need to design an algorithm which will allow prediction of CT-c changes compatible with ILD-RA with a high probability. Hopefully, this will enable treating patients with ILD-RA early, with possible halting of the progression of ILD-RA toward pulmonary fibrosis.

AUTO1-0709
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

CLINICAL EFFECTIVENESS AND RETENTION RATE OF CERTOLIZUMAB PEGOL IN THE TREATMENT OF RHEUMATOID ARTHRITIS: RETROSPECTIVE ANALYSIS FROM THE MULTICENTRIC ITALIAN REGISTRY LORHEN.

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[8]Rheumatoloy, Outside Clinic, Novara, Italy

Background

Certolizumab pegol (CZP) is widely used in clinical practice to treat rheumatoid arthritis (RA). CZP efficacy and safety has been evaluated in RCTs, but real-life data are still lacking. The aim of the study is to analyse the effectiveness and drug persistence of CPZ in a large multicenter cohort of RA patients.

Method

We extracted from the Italian LORHEN registry data on all RA patients treated with CZP as first- and second-line biologic drug between December 2010 and April 2017. Drug survival was evaluated by the Kaplan-Meier method and compared according to CZP line of treatment by a stratified log-rank test. EULAR good/moderate response and DAS28 LDA/remission rates were analysed at 12 and 24 months of treatment.

Results

The analysis included 193 RA patients (155 fist-line, 67.9% female, mean age [±SD] 53.9 [±13.5] years, mean disease duration 9.1 [±9.6] years, mean DAS28 4.61 [±1.45], 123/171 positive for rheumatoid factor, 84/118 positive for ACPA, 59% receiving CZP combined with methotrexate). CZP 5-year retention rate was similar in first- and second-line users (43.5% vs 40.5%, respectively; p=0.984). No significant differences were observed in EULAR good/moderate response rates and DAS28 LDA/remission rates between first- and second-line at both 12 (respectively 62.8% vs 54.5%, p=0.82; 55.7% vs 48.5%; p=0.455) and 24 months (respectively 66% vs 60.7%, p=0.65; 56.4% vs 50%; p=0.545).

Conclusion

In a real-life setting, the 5-year drug survival of CZP was over 40%. Similar response rates were observed in first- and second-line treated RA patients.

AUTO1-0284
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

PHASE I/II CLINICAL DEVELOPMENT OF THE FULLY HUMAN IMMUNOCYTOKINE DEKAVIL (F8IL10) IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

M. Galeazzi[1], G. Sebastiani[2], P. Sarzi Puttini[3], O. Viapiana[4], R. Voll[5], J. Dudler[6], E. Selvi[1], M. Bardelli[1], S. Finzel[5], R. Talotta[3], P. Zufferey[7], C. Specker[8], F. Bootz[9], A. Dekavil Study Group[10]
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Background

Dekavil, consisting of the inflammation targeting antibody F8 fused to interleukin-10, has the potential to enhance therapeutic activity at the site of disease while sparing healthy tissues.

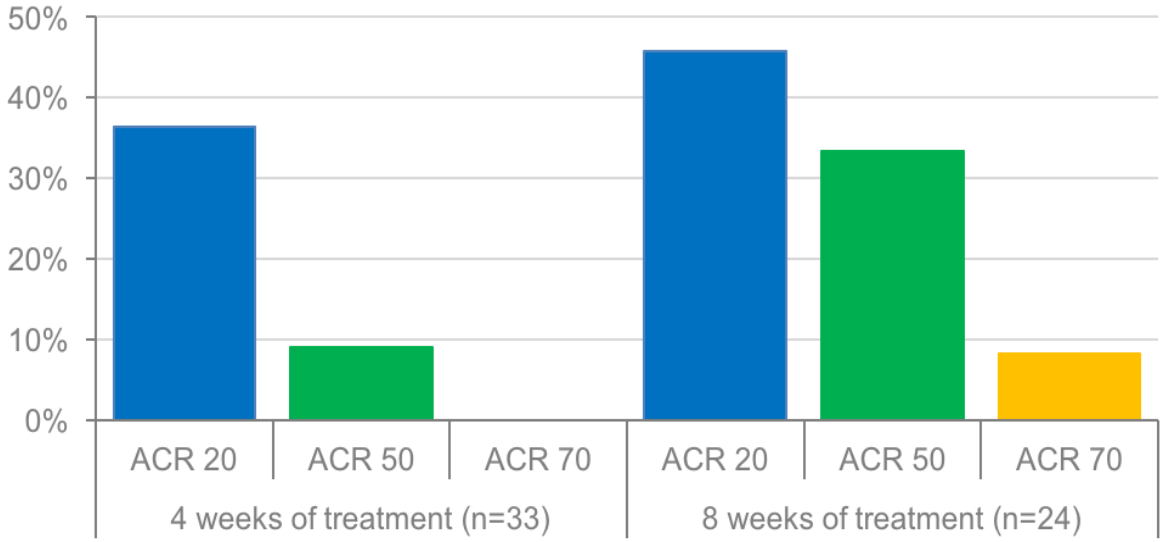
Method

A phase 1 dose escalation study exploring safety, tolerability was recently completed. A multicenter, double-blind, placebo-controlled phase 2 trial assessing therapeutic activity at two dose levels (Dekavil 30 or 160 µg/kg plus MTX) is currently ongoing.
Both trials include patients with active RA despite MTX therapy, who failed anti-TNF treatment. Dekavil is administered by weekly *s.c.* injections in combination with a fixed dose of MTX for up to 8 weeks.

Results

The phase 1 study studied cohorts with doses up to 600µg/kg and an MTD was not reached. One subject (450µg/kg) experienced a DLT (G2 purpura) accompanied by a SAE (G2 dyspnea, not drug related). Mild injection site reactions were the most frequent observed adverse events (60%). Two cases of drug related anemia were reported (G3/G2; 160µg/kg/ 450µg/kg). All adverse reactions resolved completely. The fraction of patients revealing an ACR response increased from 36.4% after 4 doses to 45.8% after 8 doses. Two patients benefited from an ACR70 for more than 12 months after the last

drug administration.



The phase 2 study has so far enrolled 25 out of 87 patients and neither SAEs, SUSARs nor deaths have been recorded.

Conclusion

The currently available data suggest that Dekavil is generally safe and well tolerated in the study population and may be a promising novel therapeutic for the treatment of RA.

AUTO1-0853
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

THE ROLE OF POST-PROCESSING TECHNIQUES IN MULTI-STAGE DIFFERENTIAL DIAGNOSIS OF LUNG GROUND-GLASS OPACIFICATION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSHPOLIPID SYNDROME

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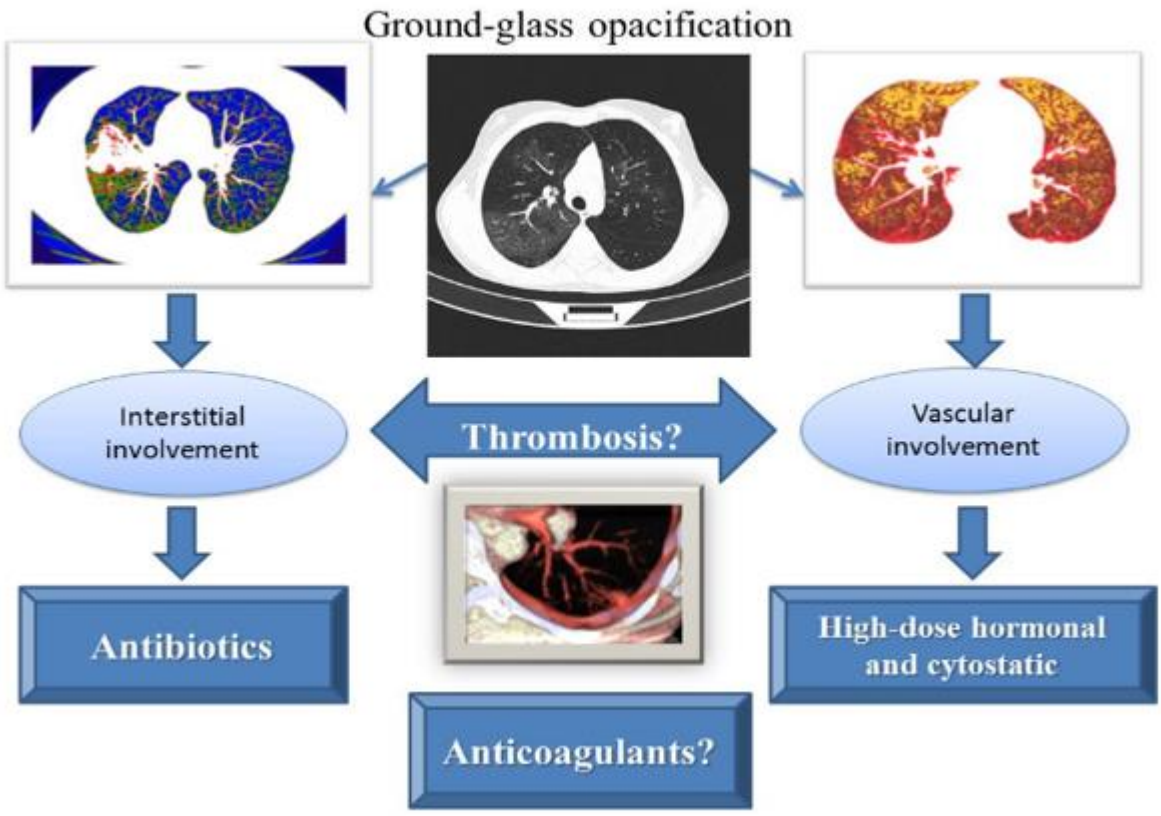
Background: Due to polymorphism of pulmonary pathology in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) ground-glass opacification (GGO) requires a multi-stage differential diagnosis the result of which will significantly affect the treatment regimen (Image №1).
Objectives: The aim of this study was to assess the role of post-processing techniques (PPTs) for differentiating between interstitial and vascular involvement in SLE patients with GGO on CT scans.
Methods: 120 SLE patients, aged 39.5 ± 13.7, were administrated a complex of laboratory, pulmonary function and imaging tests. It is the first time when PPTs such as MPR (Multiplanar reformations), MIP (Maximum intensity projection), mIP (Minimum intensity projection) and color mapping were used for differential diagnosis in patients with SLE. Reconstructed scans were compared with native CT scans, CT angiograms and perfusion scans done by three diagnosticians.
Results: Statistics showed that the mean area under the receiver operating characteristic curve value increased significantly from 0.713 without the PPTs to 0.925 with the PPTs ($P < 0.05$) in differentiating between vasculitis and pneumonia infiltration and from 0.527 without the PPTs to 0.724 with the PPTs ($P < 0.05$) in detecting thrombosis.
Conclusion: PPTs can be a useful addition to native CT scans in detecting early signs of pulmonary vasculitis, differentiating between vasculitis and pneumonia infiltration and evaluation of treatment-related changes. It equips radiologists to more easily detect areas with thrombosis especially thrombosis in situ due to pulmonary vasculitis.
Image №1. Multi-stage differential diagnosis of GGO in patients with SLE and APS.


Ground-glass opacification
Interstitial involvement
Thrombosis?
Vascular involvement
Antibiotics
Anticoagulants?
High-dose hormonal and cytostatic

AUTO1-0334
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

SARCOIDOSIS AND SJOGREN'S SYNDROME, A CONTROVERSIAL ASSOCIATION: ABOUT 7 CASES AND A SYSTEMATIC REVIEW OF THE LITERATURE

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Background

Sarcoidosis and Sjogren's syndrome (SS) are systemic dysimmune diseases, with heterogeneous clinical presentations. However, both conditions share numerous symptoms, in particular sicca syndrome. Hence, sarcoidosis is usually considered as an exclusion criterion for SS, as defined in SS classification. However, we and others have observed several cases where patients displayed clinical and paraclinical arguments in favour of both diagnoses. Herein, we hypothesized that sarcoidosis and SS may coexist in a same patient, beyond classification considerations.

Method

In this study, we collected all the cases presenting with both a diagnosis of sarcoidosis and SS in the Department of Internal Medicine and Multi-Organic Diseases (MIMMO) in Montpellier and in the literature, through a systematic review. The diagnosis of sarcoidosis was supported by a suggestive clinico-radiological picture and the presence of histological evidence of non caseating granulomas. The diagnosis of SS was based on the 2002 and/or 2016 classification criteria.

Results

In our department, we retrospectively found 7 cases of an association between sarcoidosis and SS. Through a systematic review of literature, we identified 52 other cases of this association reported to date. Interestingly, the majority of these patients presented with systemic multi-visceral sarcoidosis, whereas SS was restricted to a glandular expression.

Conclusion

Our work suggests that sarcoidosis and SS may coexist, albeit infrequently. Hence, beyond nosological controversy, such an association should be considered, since it may lead to specific management and follow-up of patients.

AUTO1-0293
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

DIAGNOSTIC PERFORMANCE OF AUTOANTIBODIES TO PEPTIDYL ARGININE DEIMINASE (PAD) 3 AND 4 IN RHEUMATOID ARTHRITIS

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Background

Anti-citrullinated protein antibodies (ACPA) are important markers in the diagnosis of rheumatoid arthritis (RA) and are part of the classification criteria. However, there is a strong need for additional markers with diagnostic and prognostic value. Antibodies to PAD3 and PAD4 have been reported in the sera of RA patients. This study analyzed the prevalence and diagnostic performance of anti-PAD3 and anti-PAD4 antibodies.

Method

The cohort consisted of 1473 subjects, including 640 RA and 833 controls (636 subjects with other diseases and 197 healthy volunteers). Anti-PAD3 and PAD4 antibodies were measured using bead based immunoassays (research use only, Inova Diagnostics, San Diego, US). ACPA consisted of anti-CCP2 (ThermoFisher, Upsala, Sweden).

Results

Anti-PAD4 antibodies were observed in 35% RA subjects (223/640) and anti-PAD3 antibodies were detectable in one third of them (12%, 77/640), a finding consistent with previous study in RA. In the control group, the prevalence of anti-PAD4 and anti-PAD3 antibodies ranged from 1-7% and from 0-2%, respectively, indicating high specificity (Table 1). When stratified by ACPA status, the prevalence of anti-PAD4 and anti-PAD3 antibodies was 43% and 13%, among anti-CCP positive RA subjects and 19% and 7% among anti-CCP negative RA subjects, respectively.

Table 1. Diagnostic performance of anti-PAD4 and anti-PAD3 antibodies.

Subject group	Anti-PAD4	Anti-PAD3
Rheumatoid Arthritis	35% [223/640]	12% [77/640]
Systemic lupus erythematosus	7% [27/369]	2% [7/369]
Sjogren`s Syndrome	3% [2/64]	0% [0/64]
Autoimmune thyroid/hepatitis	0% [0/42]	0% [0/42]
Idiopathic inflammatory myopathies	7% [2/29]	0% [0/29]
Systemic sclerosis	9% [3/33]	3% [1/33]
Other autoimmune rheumatic diseases	0% [0/14]	0% [0/14]
Primary fibromyalgia	1% [1/85]	0% [0/85]
Normal Healthy	2% [3/197]	0% [0/197]

Conclusion

In our cohort, anti-PAD4 and anti-PAD3 antibodies were found more frequently in RA patients compared to controls with high specificity. Our data also confirm that anti-PAD3 antibodies characterize a subpopulation of patients with anti-PAD4 antibodies that are highly specific for RA.

AUTO1-0737
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

ARTHRITIS IN PRIMARY SJOGREN'S SYNDROME: CHARACTERISTICS, OUTCOME AND TREATMENT FROM FRENCH MULTICENTER RETROSPECTIVE STUDY

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Background

The aims of our study were to describe the characteristics and the outcome of primary Sjögren Syndrome (pSS) associated arthritis and to compare the efficacy of different therapeutic regimen, like hydroxychloroquine (HCQ), methotrexate (MTX) and rituximab (RTX).

Method

We conducted a retrospective study using Club Rhumatisme and Inflammation (CRI) and French Internal Medicine Society (SNFMI) networks. All patients with a diagnosis of primary Sjögren's Syndrome (pSS) and at least one clinical and/or echographic synovitis were included. Patients with synovitis (cases) were compared to pSS patients without synovitis (controls).

Results

57 patients (93% women) were included with a median age of 54 years [45-63]. Patients with synovitis had more frequently lymph node enlargement (12.3% vs. 1.8%, p=0.007). There was no difference concerning other pSS systemic manifestations, CRP levels, rheumatoid factor and CCP-antibodies positivity. Among 57 patients with synovitis, 101 lines of various treatments have been used during the follow-up of 40 [22.5-77] months. First line treatment consisted in steroids alone (3.5%), steroids in association (79%) with HCQ (49%), MTX (35%), RTX (5.3%) or other immunosuppressive drugs (7%). HCQ, MTX, and RTX were associated with a significant reduction of tender and swollen joint count, and a significant steroids-sparing effect. No difference could be shown for the joint response between these treatment regimens.

Conclusion

pSS articular manifestations may include synovitis which could mimic rheumatoid arthritis but differ by the absence of structural damage. Even if the use of HCQ, MTX, and RTX seem to be effective for joint involvement, the best regimen remains to be determined.

AUTO1-0751
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

TOWARDS A BETTER UNDERSTANDING OF CHILDHOOD SJOGREN SYNDROME (CSS): EVALUATION OF THE 2016 ACR/EULAR CLASSIFICATION CRITERIA FOR SJOGREN SYNDROME

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Background

Clinical presentation of childhood Sjögren syndrome (cSS) differs from adults : dryness is less frequent while recurrent parotitis is more common. We evaluated the applicability of adult criteria for cSS.

Method

Retrospective chart reviews for cSS subjects <18 years, applying the 2016 ACR/EULAR SS classification criteria through REDCap database.

Results

To date 86 subjects, 91% female, mean onset age 11.6 y, from 11 centers in 4 countries were included. Twelve (14%) had associated disease (9 SLE, 2 uveitis, 1 subacute cutaneous lupus); 51% had parotitis, 50% dry eyes, 48% dry mouth, 45% arthralgias, 24% lymphadenopathy, 23% arthritis, 14% cytopenias, 14% fevers, 13% cutaneous vasculitis, 10% weight loss, and <10% each, recurrent vaginitis, myositis, pulmonary, renal, or neurologic manifestations. Only 3 had testing 5 items of the 2016 ACR/EULAR criteria. Most (95%) had testing for anti-SSA, but only 50% minor salivary gland (MSG) biopsy, Schirmer testing 51%, unstimulated whole saliva flow (UWSF)13%, or ocular surface staining (OSS)19%. While 96.5% were missing at least one data point, 27 of 86 children (31%) met the 2016 ACR/EULAR classification criteria for SS. Of these: 25 (93%) had positive anti-SSA; 16 (59%) MSG biopsy; 21 (78%), Schirmer test; 2 (7%) UWSF; and 1 (4%) OSS. Of the 59 not meeting criteria: 39 (66%) had positive anti-SSA; 6 (10%) MSG biopsy; 6 (10%) Schirmer test; and 2 (3%) UWSF.

Conclusion

The 2016 ACR/EULAR SS criteria are not routinely applied to cSS making retrospective assessment difficult. Prospective study defining cSS criteria is needed for early diagnosis and better treatment.

AUTO1-0283
RHEUMATOID ARTHRITIS AND SJOGREN SYNDROME AND LUNG INVOLVEMENT

NEUTROPHIL EXTRACELLULAR TRAPS ARE ASSOCIATED WITH THE PATHOGENESIS OF INTRA-ALVEOLAR HEMORRHAGE

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Background

Intra-alveolar hemorrhage (IAH) is defined by the presence of red blood cells from capillaries or venules within the alveoli leading to respiratory distress with limited therapeutics. IAH may have many immune or non-immune causes and is pathologically characterized by capillaritis. Neutrophil Extracellular Traps (NETs) are nuclear web-like structure decorated with granular protein released from activated neutrophils (PMNs). Although protective against infections, these NETs are also injurious to tissue.

Method

We used a murin lupus model of pristane-induced IAH to investigate whether NETS had a pathological role in IAH. NETs were characterized with immunofluorescence stainings of deoxyribonucleic acid, neutrophil elastase and citrullinated histones.

Results

We demonstrate that pristane promotes NETs formation in plasma and alveoli. We then directly target NETs with inhalations of deoxyribonuclease-1 (DNase-1), a well-known mucolytic drug which is commonly used in cystic fibrosis patients. DNase-1 inhalation prevents NETs accumulation in alveoli, reduces IAH lesions, improves arterial oxygen saturation and survival.

Conclusion

These data suggest that NETS form in the lungs during pristane-induced IAH, contribute to the disease process, and thus could be targeted to prevent or treat IAH. DNase-1 inhalation therapy could be an interesting adjuvant therapy in IAH.

AUTO1-0875
SMALL MOLECULES: BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 1

TLR4 AND COMPLEMENT C3 AUGMENT ALTERNATE B CELL ACTIVATION IN EARLY PHASE OF DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS

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[2]University of Pécs - Clinical Center, Department of Rheumatology and Immunology, Pécs, Hungary

Background

B-cell activation is an early event in the pathogenesis of systemic sclerosis (SSc) but the underlying mechanism remains elusive. Our goal was to find new signaling pathways which may link the vascular injury related danger signals and B cell activation in the early phase of SSc.

Method

Peripheral blood CD19+ B cells were purified from diffuse cutaneous SSc (dcSSc) patients (n=20) with disease duration of 1,4 (±1,1) years and healthy controls (n=9). mRNA expression of 92 PI3K pathway related genes was measured using a Taqman qPCR array and were validated by individual qPCR and flow cytometry.

Results

Gene array experiments showed upregulation of TLR4, IL4R, complement C3 and SPP1 (osteopontin) mRNA levels and downregulated FcgRIIb and CD180 (TLR4 inhibitor) mRNA in untreated dcSSC patients. Immunosuppressive therapy reduced the expression of SPP1 and IL4R two molecules, involved in alternate B cell activation, but C3 and TLR4 remained upregulated. Flow cytometric analysis also demonstrated increased C3 and TLR4 expression and diminished CD180 protein level in dcSSc B cells.

Conclusion

Vascular injury and fibrosis are linked to autoimmunity in SSc. At molecular level PI3K pathway in peripheral B cells may connect immune dysregulation to tissue damage via two danger signals such as TLR4 and intracellular complement C3. Modulating the involved PI3K signaling pathway in B cells may be of interest as future therapeutic target in dcSSc.

AUTO1-0855
SMALL MOLECULES: BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 1

PROTEOMIC ANALYSIS OF VIROKINES AND OTHER GENES SHARED BETWEEN EPSTEIN-BARR VIRUS AND THE HUMAN IMMUNE RESPONSE.

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A printed peptide array (PEPperprint.com) was used to analyze immune response to virokines and other shared genes between Epstein-Barr Virus and human the immune response. IgG response to virokines and other shared genes suggests a novel mechanism of autoimmune disease based on IgG response to virokines. Immune response to other shared genes is also reviewed. In summary, preliminary results suggest that peptide arrays have the potential to supplement or replace conventional immunologic diagnosis of autoimmune disease using differential response to viral shared genes.

AUTO1-0426
SMALL MOLECULES: BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 1

BIOMARKER DISCOVERY FOR THE SEROLOGICAL DIAGNOSIS OF ACPA/RF-NEGATIVE EARLY RHEUMATOID ARTHRITIS USING HIGH DENSITY PEPTIDE MICROARRAYS WITH POSTTRANSLATIONAL MODIFICATIONS

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Background

With a prevalence of 0.5 to 1%, rheumatoid arthritis (RA) is one of the most frequent autoimmune disorders. Treatment at early stages can significantly slow down disease progression. However, current serological diagnosis using antibodies against cyclized citrullinated peptide antigens (ACPA) or rheumatoid factor (RF) is negative in up to 30% of early RA patients. The precise knowledge of antigenic proteins and their underlying epitopes could provide the basis for innovative serological tests with a significantly higher sensitivity for the early and differential diagnosis of RA.

Method

To find novel RA biomarkers, we use high density peptide microarrays that can display large numbers of putative target proteins translated into overlapping peptides including posttranslational modifications such as citrullination and carbamylation. We developed the new SeroRA library with >100,000 linear and conformational peptides covering all known (vimentin, fillagrin, fibrinogen, α-enolase etc.) and candidate (e.g. cyclophilin A, BIP, α1-antitrypsin, clusterin etc.) RA antigens including all possible citrullinated and carbamylated sequence variants.

Results

Using this library, we screened 340 sera from RA and psoriasis arthritis patients as well as healthy individuals for RA-specific IgG and IgA autoantibodies. We found antibodies against various peptides from a number of different antigens which show a higher prevalence in early RA patients. These autoantibodies can potentially serve as biomarkers for early RA.

Conclusion

Currently, these peptides are validated and will be used for the development of a serological RA test with a higher sensitivity and specificity than the available diagnostic assays particularly in early RA disease.

AUTO1-0835
SMALL MOLECULES: BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 1

RHEUMATOID ARTHRITIS AND THYROID DYSFUNCTION: A CROSS-SECTIONAL STUDY

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Background: Much has been written about the comorbidities of Rheumatoid arthritis (RA), including those associated with the disease itself, as well as those that are secondary to its treatment. Thyroid dysfunction appears to show increased prevalence in many autoimmune diseases; however, not enough has been studied among patients with RA. Therefore, we sought investigate the association between RA and thyroid disorders.

Methods: Using the database of the Clalit Health Services (CHS) in Israel, we searched for the coexistence of RA and thyroid dysfunction diseases: hypothyroidism and hyperthyroidism. Patients with RA were paired with age and sex matched controls to compare the prevalence of hypothyroidism and hyperthyroidism in a cross-sectional study.
Chi-square and t-tests were used for univariate analysis and a logistic regression model was used for multivariate analysis.

Results: The study included 11,782 patients with RA and 57,973 age and sex matched controls. The prevalence of thyroid dysfunction diseases in patients with RA was increased compared with the prevalence in controls (16.0% and 11.7%, respectively, $P < 0.001$ in hypothyroidism; and 2.33% and 1.81%, respectively, $P < 001$ in hyperthyroidism). In a multivariate analysis RA was associated with hypothyroidism (odds ratio 1.42, 95% confidence interval 1.34-1.51), and with hyperthyroidism (odds ratio 1.27, 95% confidence interval 1.11-1.45).

Conclusions Patients with RA have a greater prevalence of hypothyroidism and hyperthyroidism than matched controls. Therefore, physicians treating patients with RA should be aware of the possibility of comorbid thyroid dysfunction and treat accordingly.

AUTO1-0605
SMALL MOLECULES: BREAKTHROUGH THERAPIES IN AUTOIMMUNE DISEASES 1

5-MER PEPTIDE, TARGETING AMYLOID PROTEINS, DISPLAYS A THERAPEUTIC "JANUS FACED" ACTIVITY IN AUTOIMMUNE, INFLAMMATORY AND NEURODEGENERATIVE MALADIES

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Background

A human CD44-derived 5-mer peptide MTADV (methionine ,threonine, alanine ,aspartic acid, valine) displays an efficient anti-inflammatory effect in Collagen-induced Arthritis (CIA) and Experimental Autoimmune Encephalomyelitis (EAE) mouse models of rheumatoid arthritis (RA) and multiple sclerosis (MS), respectively.

Method

Footpad swelling in CIA, Paralysis score in EAE, H&E staining of joint and brain sections , Mass Spectrometry to identify protein targets , nanoparticle tracking analysis to identify protein aggregation and cell culttures to study mechanism.

Results

The 5-mer peptide can substantially restore the normal anatomy and function of the damaged tissues. Delivery of the peptide ,after disease induction, either by IP injection ,or more importantly, by oral administration markedly reduced the inflammation as indicated by analysis of clinical symptoms and histopathology of the relevant organs (joint or brain). The peptide inhibition effect is autoimmune-specific and neutralizing antibodies are not generated. Mass Spectrometry analysis revealed that serum amyloid A (SAA) is a potential targets for the peptide anti-inflammatory activity . Furthermore, the peptide inhibited muscle paralysis of C. elegans worms expressing the amyloid β transgene. The peptide prevents the aggregation of pathological SAA leaving non-pathological small fragments and appears to block the accumulation of neurotoxic amyloid β oligomers.

Conclusion

SAA, which is recognized and neutralized by the peptide ,as documented by *in vitro* experiments, is highly involved not only in the pathology of RA and MS , but also in the pathologies of Inflammatory bowel disease, obesity , liver Inflammation, type 2 diabetes and Alzheimer's disease ,making these maladies potential therapeutic targets for the peptide.

AUTO1-0027
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

NICOTINE AND AUTOIMMUNITY: THE LOTUS' FLOWER IN TOBACCO

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Background

Nicotine is one of the principal components of cigarette smoke and its implication in autoimmunity has been (paradoxal and) controversial. It has been reported that our body has a pro-inflammatory response to nicotine, with an increasing of pro-inflammatory cytokines, as interleukin-12, and pro-inflammatory cells; on the other hand, an anti-inflammatory effect by activation of cholinergic pathway and therefore decreased of T cell activation, antibody response and pro-inflammatory cytokine production has been demonstrated as well. Nicotine seems to bind to different subunits of the nicotinic acetylcholine receptors, which are expressed on crucial cells of the immune system such as T and B cells, dendritic cells and microglial/macrophage.

Method

We run a bibliography research on autoimmunity and autominnunity diseases, and nicotine in Pubmed database and we select those disease that have information about it. We reviewed the role of nicotine in different autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, Behçet's disease, sarcoidosis and inflammatory bowel diseases.

Results

Nicotine, by cholinergic pathway (specially by the agonism to α7 subunit), has an anti-inflammatory environment characterized by increasing T regulatory cells response, down-regulating of pro-inflammatory cytokines and a pro-inflammatory cells apoptosis. In different diseases or in animal models (especially in different experimental autoimmune encephalomyelitis, Behçet's disease and ulcerative colitis), nicotine demonstrated serological and clinical improvements, which makes nicotine as a possible future therapy in those diseases.

Conclusion

Nicotine has a protective role in autoimmune diseases and its use has a therapy should be more investigated, using different products (patches, inhalators, etc) or even analogs.

AUTO1-0723
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

CANNABIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Recent cannabis legalization spurge has led to a remarkable increase in medicinal cannabis research. Animals models of autoimmune diseases suggest cannabis possible therapeutic effect, extracting an immuno-modulatory effect on various autoimmune diseases - including multiple sclerosis, rheumatoid arthritis and systemic sclerosis. Yet, to this day only scant number of studies have been conducted on cannabis effect on systemic lupus erythematosus (SLE). In light of the positive outcomes achieved in various autoimmune models we set out to explore the effect of cannabidiol, a non-psychotropic component of cannabis on a murine model of SLE for the first time. Cannabidiol effect on disease development was examined by proteinuria and dsDNA follow up. Additionally, we examined whether cannabidiol could extract a protective role in neuropsychiatric lupus by potentially preserving blood brain barrier integrity.

Method

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Results

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Conclusion

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AUTO1-0771
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

CANNABIS AND AUTOIMMUNITY

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Background

From ancient china up to the beginning of the 20th century, cannabis was utilized for numerous medicinal purposes. Today, cannabis is reemerging as a potential therapeutic agent for various indications, including multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease and other more. Focusing on the possible therapeutic aspects in autoimmune diseases, an immuno-modulatory effect is attributed to various cannabinoids owing to a wide expression of cannabinoid receptor type 2 (CB2R) on immune cells, from macrophages to T-cells and B-cells. Genetic variation in CB2R gene was also found to associate with several autoimmune diseases. Current animal models support cannabinoids potential as a disease modifying agent, though evidence is still preliminary. Although some presume to be safe, physicians and patients should refrain from referring to cannabis as a magical drug, since cannabis might trigger some rare and hazardous adverse effects such as schizophrenia.

Method

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Results

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Conclusion

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AUTO1-0600
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

SMOKE IN AUTOIMMUNITY: THE SMOKING GUN

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Background

The association between smoke habit and autoimmunity has been hypothesized a long time ago.Smoke has been

found to play a pathogenic role in certain autoimmune disease as it may trigger the development of autoantibodies

and act on pathogenic mechanism possibly related with an imbalance of the immune system. Indeed,

both epidemiological studies and animal models have showed the potential deleterious effect caused by

smoke. For instance, smoke, by provoking oxidative stress, may contribute to lupus disease by dysregulating

DNA demethylation, upregulating immune genes, thereby leading to autoreactivity. Moreover, it can alter the

lung microenvironment, facilitating infections, which, in turn, may trigger the development of an autoimmune

condition. This, in turn, may result in a dysregulation of immune system leading to autoimmune phenomena.

Not only cigarette smoke but also air pollution has been reported as being responsible for the development of autoimmunity.

Large epidemiological studies are needed to further explore the accountability of smoking effect in

the pathogenesis of autoimmune diseases

Method

Results

Conclusion

AUTO1-0762
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

CANNABINOID TYPE 2 RECEPTOR (CB2) ACTIVATION IN NEURO-IMMUNE MODULATION AT BLOOD BRAIN BARRIER

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Background

Previous studies have shown that the receptor-mediated cannabinoid system during neuroinflammation can produce potent neuroprotective and anti-inflammatory effects. Little is known about how selective activation of CB_2 affects the activated state of the brain endothelium and blood–brain barrier (BBB) function during neuroinflammation.

Method

Results

Using human brain tissues and primary human brain microvascular endothelial cells (BMVEC), we demonstrate that the CB_2 is highly upregulated during HIV infection and inflammatory insults. In vitro CB_2 agonists increased barrier tightness and increased the amount of tight junction proteins in BMVEC, decreased adhesion/migration of monocytes across BBB models and expression of adhesion molecules in BMVEC treated with proinflammatory mediators. These results were further confirmed in vivo where CB_2 agonists attenuated adhesion to and migration of leukocytes across the BBB (assessed by intravital microscopy), diminished expression of adhesion molecule and attenuated BBB 'leakiness' in mouse model of LPS or TNF-induced neuroinflammation. We recently identified novel CB_2 agonists which tightened BBB, diminished monocyte adhesion/migration across BBB models *in vitro* and protected BBB in animal models after oral administration. We also demonstrated that selective CB_2 activation in human leukocytes diminished their ability to engage the brain endothelium and migrate across BBB in vitro and in vivo preventing its injury.

Conclusion

Therefore, CB_2 ligands offer a new strategy for BBB protection during neuroinflammation.

AUTO1-0841
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

CANNABIS IN RHEUMATOLOGY: WHERE ARE WE NOW?

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Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterised by inflammation of the joints. Patients with RA often experience diminished health-related quality of life (HRQOL) with respect to both physical functioning and emotional state due to the pain, fatigue and disability that can result from this inflammation (1). Patients report that, from their perspective, these measures of HRQOL are more important than traditional measures of clinical disease activity (2)
People affected by RA still often describe pain as constantly present, and often rate it, on average, as “moderate” (3). The long-term prognosis for pain still is often unfavourable, even after inflammation is suppressed. Pain is associated with fatigue and psychological distress, and RA pain qualities often share characteristics with neuropathic pain (4,5). Each of these characteristics suggests key roles for central neuronal processing in RA pain. Pain processing by the central nervous system can maintain and augment RA pain, and is a promising target for future treatments. Inflammatory mediators, such as cytokines, may provoke central pain sensitisation in animal models, and both local and systemic inflammation might contribute to central pain augmentation in RA. Clinical studies have reported associations between inflammatory disease activity, as measured by DAS28, and pain sensitisation. However, associations with DAS28 might overestimate contributions of inflammation to central pain processing because patient-reported components (visual analogue scale for global health and tender joint count) are strongly influenced by pain itself. Pain sensitisation might inflate DAS28 values even in the absence of ongoing synovitis. Fibromyalgia (FM) has been reported to coexist in 25% of patients with RA, Its clinical diagnosis is not easy because FM-like symptoms are frequent, and its differential diagnosis with other causes of chronic diffuse pain is difficult (6).
The randomised controlled trials (RCTs) that underpin current DMARD usage (especially methotrexate) showed reductions in pain that were both statistically and clinically significant. However, participants still reported pain at final follow up (7,8) .
Given the number of the alternative biologic treatment options for the DMARD-IR (insufficient responder) RA population, clinicians are faced with a challenging choice regarding the optimal treatment (9). There is no randomized controlled trial (RCT) that evaluates all approved biologics simultaneously to help answer this question. The available evidence base consists of multiple placebo controlled trials and some active head-to-head comparisons.
Based on a network meta-analysis involving indirect comparison of trial findings (10), the following observations were made for DMARD-IR patients. In monotherapy, tocilizumab was associated with a greater improvement in pain and self-reported disease activity than aTNF, and was at least as efficacious regarding functional ability. The improvements in HRQOL with aTNF, abatacept and tocilizumab in combination with MTX were comparable. Improvements in HRQOL with tocilizumab as monotherapy were similar to that of tocilizumab + MTX, whereas aTNF as monotherapy was likely to be less efficacious than aTNF + MTX.
Controlled trials of treatments that target central pain processing have shown some benefit in people with RA, and might be most effective in individuals for whom central pain augmentation plays a key role.
Pain processing in inflammatory arthritis might be augmented by a range of factors that

are driven by inflammation itself, interacting with other risk factors for pain; such as , delay on diagnosis and treatment, genetic background, premorbid characteristics comorbidities and psychological status (11) . Sustained nociceptive input can lead to changes in central pain processing, and nociceptive input is increased fol- lowing local sensitisation of peripheral nerves within the joint. The clinical results derived by the use of biologic agents and the early treatment facing low disease activity or prolonged remission may change pain perception and may reduce the mechanism of central sensitazation that affects a relevant number of RA patients.

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AUTO1-0602
SMOKE, SMOKING, NICOTINE AND AUTOIMMUNE DISEASES

SMOKING AND THE INTESTINAL MICROBIOME

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Background

Studies are emerging alluding to the role of our microbiome in the pathogenesis of diseases. Intestinal microbiome is susceptible to the influence of environmental factors such as smoking, and recent studies have been introducing microbiome alterations in smokers.
Our aim was to review the literature regarding the impact and relationship of smoking with the intestinal microbiome.

Method

A literature review of publications in PUBMED was performed using combinations of the terms “Intestinal/Gut/Gastrointestinal/Colonic” with “Microbiome/Microbiota/Microbial/Flora” and “Smoking/Smoker/Tobacco”. We selected studies that were published between the years 2000-2016 as our inclusion criteria.

Results

Observations and studies suggest that the composition of the intestinal microbiome is altered due to smoking. In these studies, *Proteobacteria* and *Bacteroidetes* phyla, as well as the genera *Clostridium*, *Bacteroides*, *Prevotella* and members of the Lachnospiraceae were increased in smokers, while *Actinobacteria* and *Firmicutes* phyla as well as the genera *Bifidobacteria* and *Lactococcus* were decreased. Smoking also decreased the diversity of the intestinal microbiome. Mechanisms that have been suggested to explain the effect of smoking on the intestinal microbiome include: Oxidative stress enhancement, alterations of intestinal tight-junctions and intestinal mucin composition, and changes in acid-base balance. Interestingly, some smoking-induced alterations of the intestinal microbiome resemble those demonstrated in conditions such as inflammatory bowel disease and obesity. Further studies should be performed to investigate this connection.

Conclusion

Smoking has an effect on the intestinal microbiome and may alter its composition. This interaction may contribute to development of intestinal and systemic diseases, particularly inflammatory bowel diseases.

AUTO1-0527
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

HYPERPROLACTINEMIA IN PATHOGENESIS OF AUTOIMMUNE INFERTILITY

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Background

Infertility is frequent in autoimmune thyroiditis (AIT), which is the main cause of hypothyroidism in childbearing age. AIT patients typically develop hyperprolactinaemia (HPRL) caused by prolactoliberin effect of thyroliberin, which provokes hypogonadism and even prolactinomas.

Method

We examined 151 patients with AIT and hypothyroidism accompanied by HPRL aged 6 to 77 years: women - 119 (age 33.5±1.3), men - 32 (age 30.1±2, 9). In 20.5% was comorbid obesity with rose striae. Blood levels of prolactin, testosterone, and TSH were checked by ELISA, and contrasted pituitary magnetic resonance imaging (MRT) performed.

Results

Prior to treatment, prolactin level was elevated to 583.3 ± 33.4 μU/ml, TSH=2.8 ± 0.1 μMIU/ml , testosterone in males 17,4 ± 2,27 nM/l, in females 1,48 ± 0,37. The normal pituitary image presented in 18.5% MRT only, adenomata - in 39.7% (7,2% were children or adolescents), heterogeneous pituitary image - in 33 , 8%, the "empty" Turkish saddle - in 53.3%; 2,6% displayed Rathke's pouch cysts, 1,3% -lipomata, 0,7% - microhypophysis. The level of prolactin in prolactinomata was 683.7±34.8, in heterogeneous pituitary image - 522.3±37.6, in normal image it was still high - 525.2 ± 40.8 μIU/ml. After treatment with levothyroxine ® and dopamine agonists, prolactin level fell to 234.15±59.4, and TSH - to 1.21±0.3 ($p<0.001$), testosterone increased in males to 19.27±3.9 and decreased in females to 1.27±0.33 ($p>0.1$). In 3 cases the microadenomata disappeared.

Conclusion

In AIT, prolactin control and pituitary MRT are recommended. While diagnosing infertile marriage, physicians should investigate thyroid function and prolactin levels in both spouses.

AUTO1-0703
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

EFFECTS OF TUFTSIN-PHOSPHORYLCHOLINE ON THE DEVELOPMENT OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS IN MICE

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Background

Multiple sclerosis (MS) is a severe autoimmune disease characterized by processes of demyelination, axonal injury and neurodegeneration. The aim of our study was to investigate the effects of tuftsin-phosphorylcholine (TPC) on the development of experimental autoimmune encephalomyelitis (EAE) using one of the best available model of MS in mice.

Method

The study was carried out on 23 adult male mice (C57BL/6). Experimental groups: 1 - control (PBS injection); 2 - EAE (the myelin oligodendrocyte glycoprotein 35–55 peptide-induced EAE model); 3 - EAE followed by TPC injection (intraperitoneal, 5 mkg per mouse, twice a week). Neurological deficit was scored as follows: 0-no disease; 1-limp of a tail; 2 - hind limb paralysis; 3-paralysis of four limbs; 4-moribund condition; 5-death. Histological staining of brain and spinal cord was carried out to identify the regions of infiltration by inflammatory cells and demyelination (staining by Nissl, hematoxylin-eosin and Luxol Fast Blue).
Determination of activated astrocytes, axonal damage and remyelination degree in the brain and spinal cord was performed by avidin-biotin immunohistochemical method. The following antibodies were used: glial fibrillary acidic protein, precursor of beta-amyloid, nestin and myelin-oligodendrocyte glycoprotein.

Results

Injection of TPC significantly delayed the development of EAE in mice. On the 14 day of EAE development the mean clinical score was 2,3 in group with EAE and 1,7 in group with EAE followed by TPC injection.

Conclusion

The effects of TPC on the morphological changes in the central nervous system in mice with EAE will be described.

AUTO1-0852
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

ANTI-CD74 AUTOANTIBODIES IN HLA-B27 POSITIVE AXIAL SPONDYLOARTHRITIS - CLINICAL AND DIAGNOSTIC VALUE

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Currently, the problem of axial spondyloarthritis' (axSpA) diagnostics is not completely solved, especially in the early stages of the diseases. Therefore, new diagnostic markers for axSpA are urgently needed. The aim of the current study was to evaluate the prevalence, sensitivity and specificity of anti-CD74 autoantibodies (anti-CD74-AB) in HLA-B27 associated axSpA in comparison with healthy controls and with Psoriatic arthritis patients (PsA).
Methods. We measured the content of IgA autoantibodies against CD74 (quantitative ELISA method (AESKU, Germany)) in serum samples from 114 HLA-B27-positive patients with active axSpA (68 persons with ankylosing spondylitis (AS) and 46 – with nonradiographic axSpA (nr-axSpA)), and in 26 age- and sex – matched patients with active PsA with axial involvement, and in 37 healthy controls without HLA-B27. Patients with AS, nr-axSpA were matched in disease activity according BASDAI and ASDAS indices, and C-reactive protein. Nr-axSpA patients had shorter disease duration as compared with AS and PsA patients ($p < 0.001$).
Results. The average concentration of anti-CD74-AB in patients with axSpA was 3.5 ± 3.0 U/ml (3.1 ± 3.0 U/ml in AS and 3.8 ± 2.9 U/ml in nr-axSpA patients), 2.1 ± 1.4 U/ml in patients with PsA ($p \geq 0.05$ compared to controls and ax-SpA)) and 1.3 ± 1.4 U/ml in healthy controls ($p < 0.05$ for the difference with ax-SpA, AS and nr-axSpA). Diagnostic values of anti-CD74-AB in axSpA (ROC-analyze results) are presented in table 1.

Table 1

Diagnostic values of anti-CD74 autoantibodies in patients with axial spondyloarthritis (ROC-analyze)

	AUC (95% CI)	Sensitivity of the test, %	Specificity of the test, %	+LR	Upper cut-off value for reference interval, U/ml	p
axSpA	0,74 (0,67-0,82)	64,4	89,2	5,9	>2,0	<0,0001
AS	0,68 (0,59-0,79)	60,3	89,2	5,6	>2,0	0,001
nr-axSpA	0,78 (0,58-0,83)	73,1	84,0	4,5	>1,73	<0,0001
PsA	0,7 (0,69-0,89)	96,1	45,9	1,8	0,7	0,005

AS - ankylosing spondylitis, axSpa - axial spondyloarthritis, PsA - psoriatic arthritis, nr-axSpA - non-radiological axial spondyloarthritis, CI - confidence interval, +LR – positive likelihood ratio.

Cut-off value of anti-CD74-AB > 2.0 U/ml in patients with axSpA showed the diagnostic sensitivity of 64.4%, specificity of 89.2%, the positive LR of 5.9, whereas in patients with nr-axSpA at concentrations of 1.7 U/ml - sensitivity 73.1%, specificity 84% and positive LR 4.5.

Conclusions. Anti-CD74-AB are strongly associated with axSpA, but not with PsA. The measurement of anti-CD74-AB can be considered as candidate biomarker in the diagnostics of axSpA and in differential diagnostics between HLA-B27 positive ax-SpA and PsA, especially in early stages of SpA.

Further studies are needed for the evaluation of anti-CD74-AB diagnostic capacity in large population.

AUTO1-0222
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

DISTURBANCES IN DIFFERENTIATION AND POLARIZATION OF PERIPHERAL BLOOD T-HELPER CELLS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background

Multiple sclerosis (MS) is an autoimmune disease targeting the central nervous system with neurodegeneration and neuroinflammation. The underlying mechanisms of MS are not fully understood yet, but CD3+CD4+ T cells (Th) are thought to be of importance in disease pathogenesis.

Method

To analyze the frequency of Th cell subsets, peripheral blood (PB) from were 44 healthy controls and 29 patients with relapsing-remitting MS was evaluated by multicolor flow cytometry. Main PB Th differentiation stages as well as maturation stages of regulatory T cells were investigated. Based on the expression of the CCR4, CCR6, CXCR3 and CXCR5 central memory and effector memory Th were subdivided into 11 subsets.

Results

No differences were found in Th differentiation stages, purified on the expression of CD27, CD28, CD45RA and CD62L, between MS patients and control group. Frequency of PB “naïve” Th cells decreased while percentage of EM Th cells gradually elevated with increasing of EDSS score. MS patients vs. volunteers contained significantly lower percentage of “naïve” Tregs, while the relative number of CM and EM Tregs were significantly higher in MS patients. Furthermore, MS was associated with decreased relative number of CXCR5–CXCR3+CCR6+CCR4– Th (Th1/Th17) in CM and EM Th subsets. The relative numbers of these Th subsets were most effective in discrimination between MS patients and control group.

Conclusion

Disturbances in Th subset composition found by us in PB from MS patients suggest that both Tregs and some subsets of Th17 and Tfh cells play a role in developing MS.

AUTO1-0275
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

INTRATHECAL SYNTHESIS OF IMMUNOGLOBULINS AGAINST NEUROTROPIC VIRUSES FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS

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Background

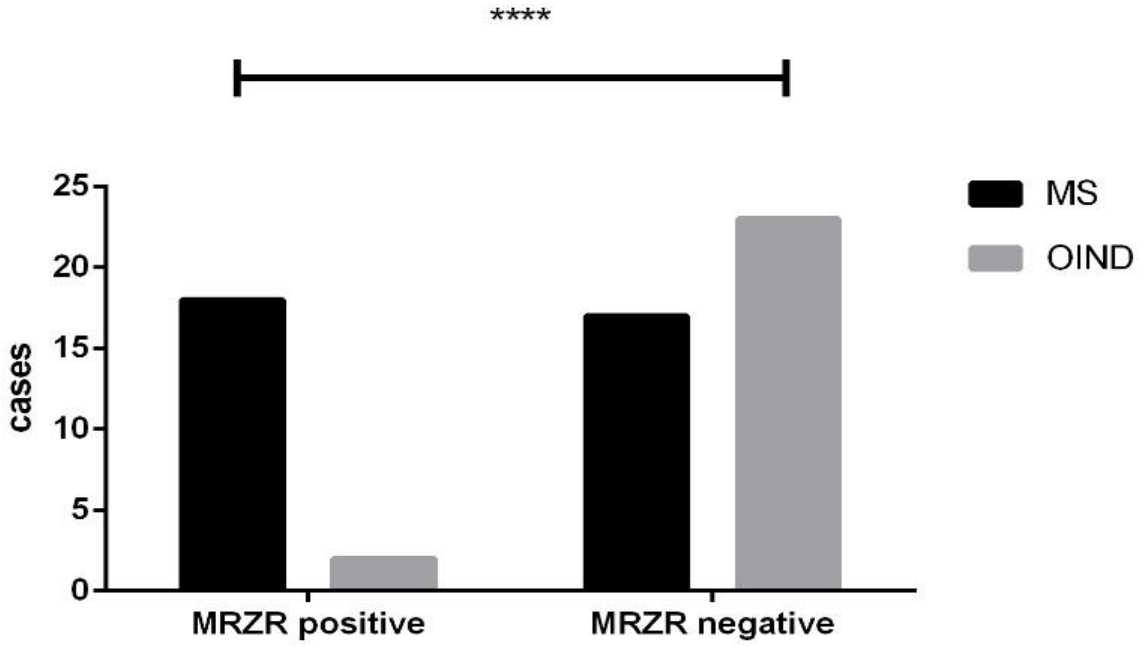
Multiple sclerosis (MS) is autoimmune disease characterized by prominent intrathecal immune response. At least partially it is directed against neurotropic viruses (Measles, Rubella and varicella Zoster) so called MRZ-Reaction (MRZR). The aim of the study was to determine the diagnostic significance of the MRZR for MS.

Method

Paired serum and CSF samples from 35 patients with MS and 25 patients with other inflammatory neurologic diseases (OIND) were tested with ELISA, Euroimmun (Germany), and biochemical analysis BioSystems S.A. (Spain). Antibody index >1.5 was scored positive for intrathecal antibody production. The result is positive in the presence of 2 or more antibodies to viral agents. All samples were examined for IgG oligoclonal bands (OCB) (Helena Biosci, UK).

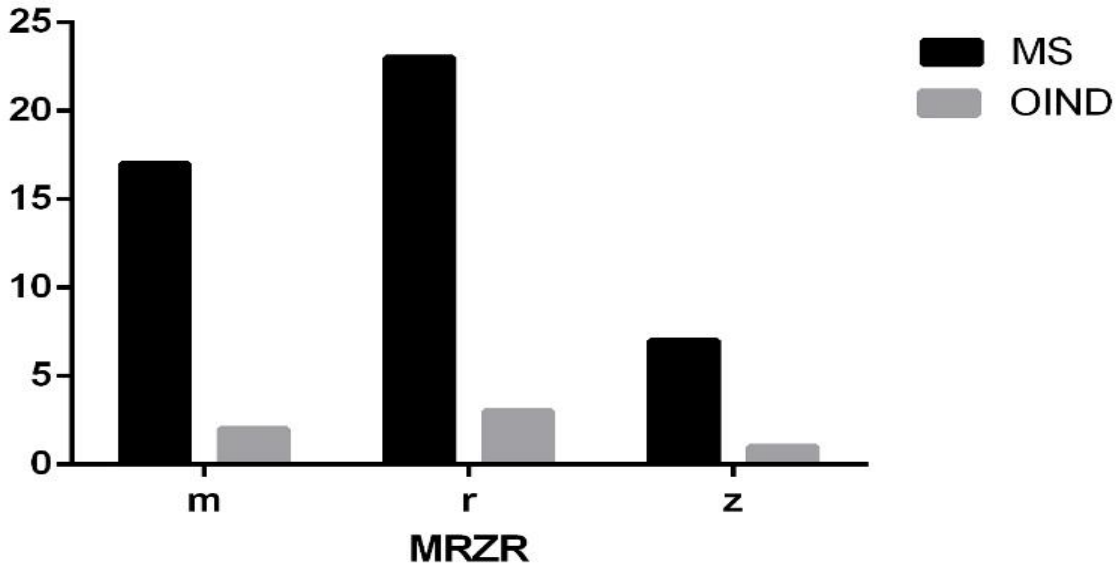
Results

Positive MRZR was found in 51.4% in patients with MS and in 8% cases in OIND group ($p < 0.0004$). This corresponds to cumulative specificity of 92% and sensitivity of 51.4%.

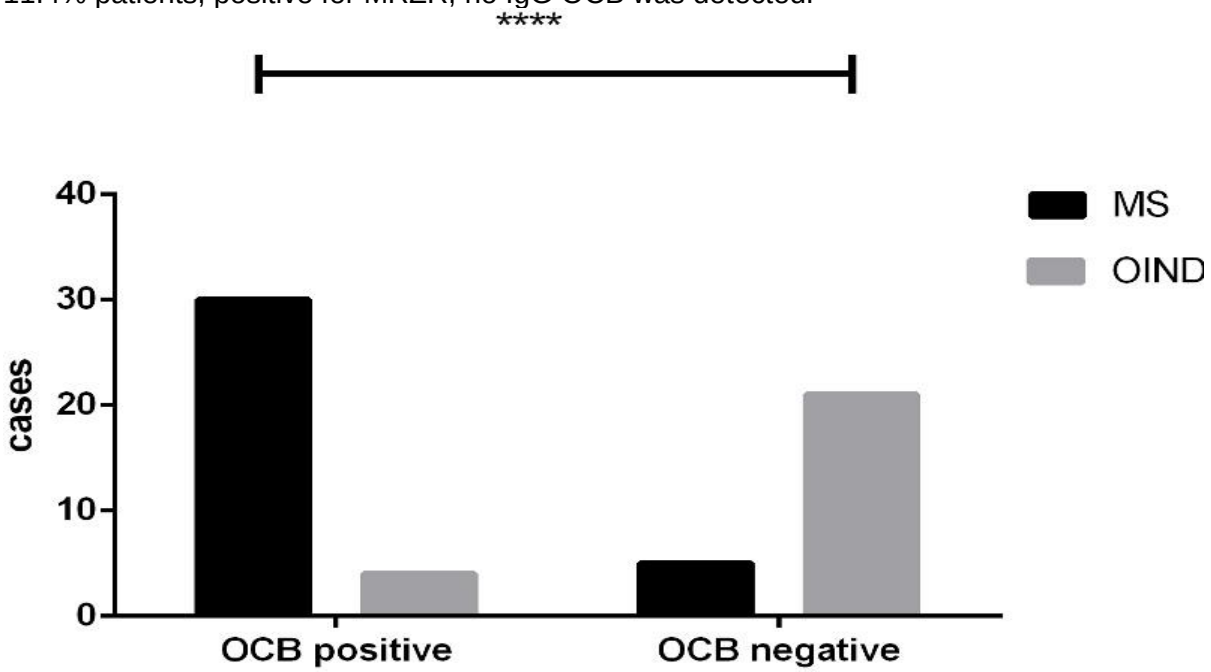


In the MS group 25.7% patients had intratecal syntesis IgG against one viral agent,

45.7% - against two and 5.7% - against three agents. Namely 45.7% patients of the MS group had anti- measles antibodies, 62.8% against rubella, 2% against zoster virus.



IgG OCB were detected in 85.7% patients with MS and in 16% of OIND group ($p < 0.0001$). This corresponds to cumulative specificity of 84% and sensitivity of 85.7%. In 11.4% patients, positive for MRZR, no IgG OCB was detected.



Conclusion

MRZR is a highly specific marker for the diagnosis of MS that is found positive among OCB-negative patients with MS.

AUTO1-0374
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

BRAIN ATROPHY AND LONG-TERM DISABILITY PROGRESSION IN MULTIPLE SCLEROSIS ARE RELATED TO CONCENTRATIONS OF FREE LIGHT CHAINS IN CEREBROSPINAL FLUID

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Background

Intrathecal activation of B-cell is the main pathological finding in multiple sclerosis (MS). B-cell activation in MS was associated with brain atrophy. Intrathecal concentration of free light chains (FLC) of immunoglobulins is one of the diagnostic biomarkers of MS. The aim of our study was to evaluate long-term prognostic significance of cerebrospinal fluid (CSF) FLC levels and their influence on brain atrophy.

Method

Long-term prognosis (LTP) was studied in 284 MS patients and brain atrophy (BA) was studied in 65 MS patients. According to FLC levels in CSF LTP patients were divided into cases with high FLC and low FLC levels. FLC concentrations were measured using ELISA in CSF and serum. In LTP Multiple Sclerosis Severity Score (MSSS) and Expanded disability scale score (EDSS) was measured at the date of the last follow-up. In BA group brain atrophy was assessed using fully automated MRI SienaX algorithm.

Results

In LTP group positive correlations were detected between EDSS and kappa-FLC in CSF (r=0,181; p=0,002), MSSS and kappa-FLC in CSF (r=0,121; p=0,044). Survival analysis revealed an increased risk for long-term progression of disability (EDSS=6.0) for high kappa-FLC in CSF (HR=2.055, p=0.026). In BA group the concentration of kappa-FLC in CSF, Q-k showed significant inversed correlation with normalized brain volume (k-FLC: r=-0.2613, p=0.0355; Q-k: r=-0.3456, p=0.013) and with normalized gray matter volume (k-FLC: r=-0.2858, p=0.021; Q-k: r=-0.3367, p=0.0157).

Conclusion

Kappa-FLC in CSF is related to long-term disability progression and also could be potential biomarker for neurodegeneration in MS.

AUTO1-0327
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

ON THE PATHOGENESIS OF PSYCHIATRIC DISORDERS IN HASHIMOTO'S THYROIDITIS

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Background

Behavioral disorders often accompany autoimmune thyroid disease, although pathogenesis of that is poorly understood.

Method

We studied 16 treated patients with clinically confirmed autoimmune thyroiditis (AIT) 18 to 78 years of age (50.3 ± 16.0), 15 women and a man, all having established psychiatric diagnoses, like schizophrenia - 13 (86%), and Alzheimer's disease, obsessive-compulsive disorder or dementia – 1 (6%) each. The most frequent psychiatric manifestations were phobias (50%), manic-depressive disorders (19%), cognitive defects (31%), depression (31%), autistic behavior (37%), mania (44%), paranoia (94%), hallucinations (94%), sleeplessness (37%), drowsiness (19%), suicide attempts (31%). 56% of them had positive family psychiatric anamnesis. We checked by ELISA their blood levels of TSH, T_3 , T_4 and autoantibodies to thyroperoxidase (antiTPO) and evaluated thyroid volume by ultrasonography.

Results

The antiTPO was highly increased [427.4± 55.7]. Thyroid hormones were normal with T_3 =1.74 ±0 .6 and T_4 =97.7± 29.0, and TSH= 2.4± 1.01, hence all patients were euthyroid to the moment of study, with their psychiatric disorders could not be explained with thyroid dysfunction. Direct correlation existed between the duration of a psychiatric illness (since primary diagnosis) and antiTPO level; and between the thyroid volume and antiTPO level by (t_{emp} = 2.9, within significance range for both pairs).

Conclusion

A relationship exists in AIT between the antiTPO level, compensatory thyroid hyperplasia and the stage at which mental disorders are recognized. It happens earlier in those having higher antiTPO levels.

AUTO1-0858
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

MEDICAL GEOGRAPHY OF AUTOIMMUNE DISEASES IN RUSSIA: BIG DATA ANALYSIS

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[1]

Background

Geographical distribution of the incidence and prevalence of autoimmune and auto-inflammatory diseases (AD) in the world largest country of Russia (RF) is extremely uneven as well as natural and anthropogenic environmental factors in its 83 regions.

Method

Research is based on correlation of the open data on prevalence and incidence of several AD (rheumatoid arthritis, thyrotoxicosis, diabetes mellitus type 1, multiple sclerosis, psoriatic arthropathy, localized scleroderma, spondylopathy, thyroid diseases (excerpt tumors) demyelinating diseases) for the period of 2008-2016. Morbidity in the RF was compared several parameters of urbanization and pollution (density of public roads with hard surface; emissions of pollutants into the atmosphere, departing from stationary sources; the number of reported cases of high pollution of surface waters; the number of public buses). Whole population, children up to 14 years old, adolescents aged 15 to 17 years, adults and retired seniors followed separately. Correlation-regression analysis and Student's test were performed with subsequent development of a model for the emergence and spread of the risk of AD.

Results

AD have a close clustering when distributed throughout the RF ($\chi 2emp = 647.948$, $v = 164$, $p<0.05$). Statistically reliable correlation exists between the density of public roads with hard surface and spreading of AD studied, emissions of pollutants into the atmospheric air and spreading of AD studied, the number of chemical trace elements (adjuvants: Al, Hg, I) in biological samples and scattering of a AD.

Conclusion

The findings suggest a statistically significant relationship between urban and environmental factors and the development and the spreading of AD.

AUTO1-0564
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

EVALUATION OF SPECIFIC IMMUNE COMPLEXES IN PATIENTS WITH SARCOIDOSIS AND LUNG TUBERCULOSIS

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Background

The role of serum immunoglobulins in the development of sarcoidosis is not clear, perhaps they participate in the formation of granuloma attaching to immune complexes (IC).

The aim of the study was to reveal the features of specific IC in patients with sarcoidosis and tuberculosis.

Method

From January to July 2017, a prospective study has been conducted at Institute of Phthisiopulmonology and St. Petersburg City Hospital №2. We included 89 patients (47 men and 42 women, 38.5 ± 9.57 years). There were 2 groups: I (n = 56) with lung tuberculosis; II (n = 33) with sarcoidosis. The control group - 19 healthy donors. Evaluation of blood plasma was carried out with the use of dynamic light scattering method with *in vitro* addition of ESAT-6, SFP-10 in the Institute of Nuclear Physics. Differences were significant at $p < 0.05$.

Results

Formation of IC with the addition of specific antigen was registered in 100% (56) cases of tuberculosis (total IC - 6.85 ± 0.37, IgG1 - 4.25 ± 0.26; IgG3 - 3.2 ± 0.16, IgE - 3.29 ± 0.25, IgG1 + IgG3 - 3.83 ± 0.28, IgG1 + IgE - 5.66 ± 0.55, IgG3 + IgE – 2.86 ± 0.5). The same time IC was identified in none of (33) cases with sarcoidosis and none of 19 healthy donors of control group ($p = 0.000...$). The diagnostic specificity 100%.

Conclusion

The significant differences in the formation of specific IC in patients with tuberculosis and sarcoidosis can serve as differential diagnostic criteria.

AUTO1-0258
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

COMPARISON OF NEW MULTI-LINE IMMUNODOT ASSAY AND ELISA FOR DETECTION OF ANTIPHOSPHOLIPID ANTIBODIES

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Background

Laboratory diagnosis of antiphospholipid syndrome (APS) is based on detection of antiphospholipid antibodies (aPLs). So main aPLs are directed against ß2-gycoprotein 1 (aß2-GP1) and cardiolipin (aCL). Traditional ELISA is challenged by new tests when antigen is absorbed on another kind of support like microbeads or membranes. The aim of our study was to compare the results of detection of aPLs by ELISA and multi-line immunodot assay (MLD).

Method

We collected the serum samples from 45 patients with ischemic strokes, 19 patients with deep vein thrombosis and 44 patients with reccurent miscarriages, 95 patients with systemic lupus erythematosus (SLE), 50 healthy donors. For detection of aPLs we used an ELISA kits produced by Euroimmun AG - Manufacturer 1 (Mr1), Orgentec Diagnostica GmbH - Manufacturer 2 (Mr2), MLD - (Medipan GmbH - Manufacturer 3 (Mr3)).

Results

When manufacturer's cut-off twas used 57 % (61/108) of patients were aPLs-positive with ELISA method and 40% (43/108) by MLD. Medium and high aPLs titers (3*cut-off) were determined in 14% of patients using ELISA kits and in 23% using Mr3 ($p = 0.03$). Antibody to aCL and aß2-GP1 IgG were more common in SLE with APS samples, comparing with SLE with aPhs (OR=5, p=0,0241).

Conclusion

Because of higher sensitivity for medium and high aPLs titers MLD can be used for confirmation of APS diagnosis. Profile of aPLs in with APS and SLE with aPhs differs: SLE with APS is associated with aCL IgG and aB2GP1 IgG, where as SLE with aPLs patients - with aCL IgM and aB2GP1 IgM.

AUTO1-0320
THE 2ND MOSAIC OF AUTOIMMUNITY SAINT PETERSBURG

THE STUDY OF ENVIRONMENTAL EXPOSURES AS A PART OF THE ASIA SYNDROME IN THE DEVELOPMENT OF SARCOIDOSIS

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Background

The prevalence of sarcoidosis is increasing, but it's etiology is still unknown. The role of adjuvants in the development of pathological inflammatory process (Autoimmune Syndrome Induced by Adjuvants - ASIA) was reflected in the work of Y.Shoenfeld (2011). The connection between ASIA and sarcoidosis in genetically predisposed individuals is an actual topic (Bindoli S., 2016).The aim of the study is to identify exogenous factors in the development of sarcoidosis.

Method

A retrospective-prospective study within the framework of the Megagrant under the leadership of Y.Shoenfeld is conducted at the Institute of Phthisiopulmonology and St. Petersburg State University. We included patients with lung sarcoidosis (n =49) diagnosed from 2014 to 2016. In 36 (73,5%) sarcoidosis I-II stages was detected, 7(14,3%) patients had Lofgren's syndrome and 6(12,2%) had generalized sarcoidosis. All patients underwent a standard examination complex and an anamnesis data collection using ASIA Research Questionnaire. Differences were significant at $p < 0.05$.

Results

The most significant risk factors are presented in Table 1.

Table 1. Risk factors in the study participants

Vaccinated study participants, *n* (%)	20 (40.8%)
Previously or currently smoking, *n* (%)	21 (42.8%)
Total allergies, *n* (%)	21 (42.8%)
Stress in the 3 years before onset, *n* (%)	**43 (87.7%)***
More than 3 pregnancies, *n* (%)	10 (20.4%)
Study participants with foreign material, *n* (%)	32 (65.3%)
Occupational hazards, *n* (%)	31 (63.2%)

As shown in Table 1, the most significant factors were stress, foreign material and occupational hazards (*p <0.05 - when comparing risk factors). Smoking, allergies and vaccination were often noted. Time between exposure to foreign material and symptoms' onset was 10,8 (±8,7) years.

Conclusion

The most significant factors in the development of sarcoidosis, according to preliminary data, are stress, foreign material and occupational hazards. Smoking, allergies and vaccination may have a significant effect, which requires further research.

AUTO1-0252
THE DIVERSITY OF AUTOIMMUNE DISEASES

MYOSITIS SPECIFIC ANTI-HISTIDYL TRNA SYNTHETASE (HISRS) AUTOANTIBODIES DISPLAY HIGH REACTIVITY AGAINST HISRS CONFORMATIONAL EPITOPES AND ASSOCIATE WITH LUNG AND JOINT INVOLVEMENT

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Background

Autoimmune myositis (rheumatic muscle inflammation), associated with interstitial lung disease (ILD) and arthritis is strongly correlated with anti-HisRS autoantibodies. The aim of this study was to investigate 1) myositis IgG reactivity against HisRS conformational epitopes 2) association between clinical manifestations and the reactivity profiles.

Method

Serum IgG was isolated using a protein G affinity column (from 25 anti-HisRS- and 19 anti-HisRS+ myositis, 24 age/gender matched healthy controls, HC). Antibody reactivity was tested by ELISA against HisRS full-length and three HisRS conformational epitopes (WHEP domain - localized in the N-terminal; HisRS without WHEP (HisRS_WHEP); and ABD – anticodon-binding domain located in the C-terminal). Correlations between diagnosis, clinical manifestations and anti-HisRS IgG reactivity were evaluated.

Results

HisRS+ myositis IgG displayed stronger reactivity against full-length HisRS and HisRS_WHEP (median 372 ng/mL and 334 ng/mL, respectively), compared to WHEP and ABD (6.38 and 6.48 ng/mL). A higher anti-full-length HisRS reactivity (>371 ng/mL) was observed in patients presenting ILD (100% of patients), arthritis (60%) and polymyositis diagnosis (PM, 90%), compared to patients with low (<23 ng/mL, ILD – 83%; arthritis – 50%; PM – 82%) or no anti-HisRS IgG reactivity (ILD - 37%; Arthritis - 30%; PM - 54%). Myositis patients with low or no anti-HisRS reactivity presented a higher percentage of DM diagnosis, skin rash and dysphagia (Figure attached).

Conclusion

This study provides evidences for an underlying role of anti-HisRS autoantibodies in myositis patients with lung and joint involvement and may therefore contribute to the development of novel targeted therapies, which will delay or prevent disease progression.

AUTO1-0594
THE DIVERSITY OF AUTOIMMUNE DISEASES

AUTOIMMUNE PATHOGENIC MECHANISMS IN AMYOTROPHIC LATERAL SCLEROSIS

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Background

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterised by a progressive death of motor neurons, resulting in fatal paralysis in a few years.The cause of ALS and the specific mechanisms of neuronal death remain unknown. However, considerable evidence supports the existence of autoimmune mechanisms contributing to pathogenesis in ALS.

Method

A systematic review was conducted using PubMed and Scopus databases and relevant literature on ALS was included.

Results

Various environmental factors have been proposed to be associated with ALS; however, the only established risk factors to date are older age, male gender, and a family history of ALS. Clinicians mostly rely on identifying the combination of upper motor neuron and lower motor neuron signs in the same body region. A definitive diagnosis is reached with a median time of about 14 months. Riluzole has been established as the only and modestly effective therapy for ALS, extending mean patient survival by 3-6 months. Immunosuppressive drugs have not altered disease progression. The use of immunoablation to abolish the neurotoxic effects of the immune response with reinfused stem cells to replenish the immune system has been proposed. The cornerstones of the management of patients with ALS are focused on symptom control and maintenance of quality of life and improve survival rate.

Conclusion

Recent developments in understanding encourage realistic hope that new treatment approaches will emerge. However, underlying mechanisms that induce generation of autoantibodies are still unknown. Their identification will allow designing rational therapies for specific molecular targets, further characterizing the role of autoimmune mechanisms.

AUTO1-0001
THE DIVERSITY OF AUTOIMMUNE DISEASES

THE APTAMER BC 007 FOR IN VIVO NEUTRALIZATION OF PATHOGENIC AUTOANTIBODIES DIRECTED AGAINST G-PROTEIN COUPLED RECEPTORS PRESENT IN PATIENTS WITH CARDIOMYOPATHY: STEPS TO A NEW TREATMENT OPTION

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The finding of functionally active autoantibodies directed against G-protein coupled receptors (GPCR, GPCR-AABs) in diseased subjects and the evidence of them being pathogenic has introduced a new class of autoimmune diseases which can be called functional autoantibody disease. Due to the patients' positivity for GPCR-AABs, cardiomyopathies such as idiopathic dilated cardiomyopathy (DCM), Chagas' cardiomyopathy and peripartum cardiomyopathy can be classified as functional autoantibody disease. For the treatment of GPCR-AAB positive DCM patients, GPCR-AAB removal by immunoadsorption has been studied with convincing patient benefit. To overcome cost and logistics problems of immunoadsorption, we introduced the aptamer BC 007 for in vivo GPCR-AAB neutralization. BC 007 neutralized in vitro beta1-AABs which were prepared from cardiomyopathy patients as well as other comorbidity-associated GPCR-AABs. The aptamer's in vivo neutralizing potency was demonstrated in animals and recently for in beta1-AAB positive humans. Due to the safety demonstrated in pre-clinical studies and a phase 1 clinical trial, BC 007 treatment of beta1-AAB positive cardiomyopathy patients would, in our view, have a comparable benefit as that seen after immunoadsorption. Consequently, steps have been taken to bring BC 007 as a drug closer to patients.

AUTO1-0606
THE DIVERSITY OF AUTOIMMUNE DISEASES

EVALUATION OF DIAGNOSIS PERFORMANCE OF ANTI-PM/SCL ANTIBODIES DETECTED BY ELISA

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Background

Anti-PM/Scl antibodies are rare autoantibodies associated with systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM) and more specifically with PM/SSc overlap syndromes. The objective of this study is to evaluate retrospectively the clinical value of anti-PM/Scl antibodies detected by ELISA.

Method

This study was performed on sera obtained from patients followed in different clinical departments (HCL, France) during 2013 to 2017. Fourty three sera were found to be positive for anti-PM/Scl antibodies using an ELISA technique (ELISA PM1-alpha peptide, Euroimmun) with the manufacturer's cut-off value of 20 AU/mL. Sera were also analyzed by indirect immunofluorescence (IIF) on HEp2 cells (Biorad) and some samples were evaluated by dot blot (Euroimmun).

Results

Among the 43 positive sera, 56% of the patients suffered from SSc, PM, DM or overlap syndromes, 14% from connective tissue diseases (mostly lupus) and 30% from other diagnosis. Using a cut-off of 50 AU/mL, 75% of positive samples were associated with SSc, PM, DM or overlap syndromes and only 8% with connective tissue diseases. Sera from patients with other diagnosis and a titer between 20 and 50 AU/mL were analyzed by dot blot and were found to be negative. Typical staining IIF pattern was more frequently found with samples found to be positive by ELISA using a cut-off above 50 AU/mL (85% *versus* 32%).

Conclusion

In conclusion, a better diagnosis performance in term of specificity for anti-PM/Scl antibodies was obtained by the combination of ELISA using a cut-off of 50 AU/mL and IIF with the identification of a speckled and nucleolar staining pattern.

AUTO1-0277
THE ENIGMAS OF SYSTEMIC SCLEROSIS

CHROMOSOMAL ABERRATIONS ARE ASSOCIATED WITH DISEASE SEVERITY IN A MOUSE MODEL OF BLEOMYCIN-INDUCED SCLERODERMA

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Background

Scleroderma (SSc) is a connective tissue disease characterized by inflammation and fibrosis. Autoantibodies against chromosome associated proteins were observed in SSc patiens, however genotoxic events have never been evaluated. We Investigated the presence of chromosomal aberrations and micronuclei (MN) in peripheral lymphocytes in a SSc mouse model induced by bleomycin (BLM).

Method

Balb/c mice (n=20 per conditions) were treated with BLM or PBS (control) for 14 days. Proteinuria was measured weekly. At day 15 mice were sacrificed. The MN assay was performed on peripheral lymphocytes cultured with cytochalasin B (10 µg/ml) for 24 h. A minimum of 1000 binucleated cells/mouse were scored.The antikinetochore (CREST) staining was used to determine the origin of MN observed.

Results

BLM treated mice showed lung and skin fibrosis. 17 out of 20 mice developed acute renal involvement with mean proteinuria levels of 730±48 mg/dl. In comparison with the control mice, a significant increase in MN number was observed in BLM treated mice (57,8±4,4 vs 6,3±0,6, $p<0.05$). Also CREST staining was higher (16,4±1,1 vs 3,7±0,7, $p<0,025$) indicating that MN arised from lagging chromosomes. A correlation between the presence of CREST stained MN and renal failure, lung and skin fibrosis was observed (respectively R=0,4095; R=0,7507 and R=0,9471).

Conclusion

This study provides experimental evidence that significant chromosomal aberrations seem to be related to the severity of disease in a mouse model of SSc. Further investigations on lymphocytes obtained from SSc patients could be matched with results observed in mouse to confirm the relationship between severity of the disease and chromosomal abnormalities.

AUTO1-0351
THE ENIGMAS OF SYSTEMIC SCLEROSIS

SERUM TRYPTOPHAN AND KYNURENINE LEVELS ARE ALTERED IN SYSTEMIC SCLEROSIS WITH DISTINCT CLINICAL AND AUTOANTIBODY ASSOCIATIONS

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Background

Systemic sclerosis (SSc), a fibrotic illness without specific biomarkers, has anecdotal reports of elevated tryptophan (Trp) metabolites. Indoleamine dioxygenase (IDO) induced by IFN-gamma/IL-1 degrades Trp to Kynurenine (Kyn) and is implicated in immune regulation. Serum Kyn, Trp and Kyn/Trp ratios of SSc are explored for their associations with clinical features and anti-nuclear-autoantibodies.

Method

Serum Kyn, Trp and Kyn/Trp ratio by HPLC and neopterin by ELISA were measured in 97 SSc patients and 10 healthy controls (HC). Serial samples were obtained for 40 pts. Associations with disease characteristics were evaluated.

Results

Kyn 1.3 µmol/L (95%CI 1.01 -1.7) and kyn/trp ratio 22.5 µmol/mmol (95%CI 17.9-27.01) of HCs was significantly lower than that of SSc; 2.1 µmol/ (p=0.037) and 44.1µmol/mmol (p=0.059) lcSSc and 2.4 µmol/L (p=0.002)and 56.8µmol/mmol (p = 0.004) dcSSc. Kyn, Trp or Kyn/Trp show consistent levels in the respective SSc groups over time. IDO activity, Kyn/Trp ratios, strongly correlated with neopterin levels in all autoantibody positive groups; anti-topoisomerase (ATA+) r=0.71 (p<0.001), anti-centromere (ACA+) r=0.86 (p<0.001) and anti-RNA-polymerase III (ARA+) r=0.83 (p<0.0001). Malignancies among the ARA+ were 23% versus ATA; 12% and ACA 8%. Higher Kyn/Trp ratio among ARA+ without lung fibrosis; mean 67 µmole/mmole versus ARA+ with lung fibrosis mean 50 µmole/mmole was of no significance (p=0.23).

Conclusion

These data suggest dysregulated Trp metabolism influences immune cell function and fibrosis; particularly in the diffuse SSc subset, and in ARA+ patients. The pathogenetic relevance and stability of these analytes over time may make markers of Trp metabolism useful in SSc stratification.

AUTO1-0099
THE ENIGMAS OF SYSTEMIC SCLEROSIS

ASSOCIATION OF OCCUPATIONAL EXPOSURE TO SILICA AND ORGANIC SOLVENTS WITH FEATURES OF SYSTEMIC SCLEROSIS.

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Background

Occupational exposure is reported as playing a substantial causative role in systemic sclerosis (SSc). We compared the characteristics of SSc in patients with and without occupational exposure to crystalline silica/solvents.

Method

In all, 142 patients with SSc were enrolled in this prospective study. An expert committee performed blind evaluation of occupational exposure to crystalline silica/solvents.

Results

Patients exposed to crystalline silica more often exhibited: diffuse cutaneous SSc (P = .02), digital ulcers (P = .05), interstitial lung disease (P = .0004), myocardial dysfunction (P = .006), and cancer (P = .06). Patients exposed to solvents more frequently developed: diffuse cutaneous SSc (P = .001), digital ulcers (P = .01), interstitial lung disease (P = .02), myocardial dysfunction (P = .04), and cancer (P = .003); in addition, these patients were more frequently anti-Scl 70 positive and anticentromere negative. Under multivariate analysis, significant factors for SSc associated with exposure to silica/solvents were: male gender (odds ratio 19.31, 95% confidence interval 15.34-69.86), cancer (odds ratio 5.97, 95% confidence interval 1.55-23.01), and digital ulcers (odds ratio 2.42, 95% confidence interval 1.05-5.56).

Conclusion

Occupational exposure to crystalline silica/solvents is correlated with more severe forms of SSc characterized by: diffuse cutaneous involvement, interstitial lung disease, general microangiopathy (digital ulcers and myocardial dysfunction), and association with cancer. Occupational exposure should be systematically checked in all patients with SSc, as exposed patients seem to develop more severe forms of SSc.

AUTO1-0574
THE ENIGMAS OF SYSTEMIC SCLEROSIS

SEROTONIN: THE NEW MARKER OF SKIN AND LUNG INVOLVEMENT IS SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis (SSc) is a rare chronic disease which is chararacterised by collagen deposits, primary in skin and lungs, but it can also affect any other organ. Recent studies showed that serotonin antagonist can prevent vascular manifestations and Raynaud's phenomenon in SSc, although exact mechanism is not clearly understood. We wanted to investigate the correlation of serum levels of serotonin with disease manifestations in patients with SSc.

Method

We measured serum levels of serotonin in 30 patients with SSc. Patients were 41-79 years old, their average disease duration was 9.6 years and majority of them were females. Serotonin values were analysed in correlation with clinical and laboratory paramethers, such as modified Rodnan skin score (mRSS), digital ulcers (DU) and spirometry paramethers (FEV1, FVC, DLCO). Serotonin values in healthy controls are still in process.

Results

Average value of serotonin was 192.8 and the highest values of serotonin were documented in patients with refractory DU. Unfortunately this correlation was not statisticaly significant. Higher serum levels of serotonin were in correlation with higher mRSS (p= 0.017). We also found out that higher levels of serotonin correlated with lower values of FVC (p=0.072), which was not proved with other parameters.

Conclusion

Our study proved serotonin as potential marker of skin fibrosis in patients with SSc. Further studies on its role in lung manifestations of SSc are needed.

AUTO1-0744
THE ENIGMAS OF SYSTEMIC SCLEROSIS

ARTICULAR INVOLVEMENT IN SYSTEMIC SCLEROSIS: COMPARISON OF CLINICAL, RADIOGRAPHIC AND SONOGRAPHIC FINDINGS

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Background

Joint involvement in Systemic Sclerosis (SSc) is frequent and varied. We study US synovitis and its correlation with clinical synovitis, radiological erosions and organ involvement.

Method

In a prospective cohort of SSc patients, tender and swollen joint counts, DAS28-CRP, hand US sonographies, X-ray hand views, as well as respiratory, cardiac, cutaneous and renal characteristics were assessed.

Results

54 patients were included with a median age of 59 years (27-81), 45 women (83%), with a diffuse cutaneous subtype in 13 patients (24%). 23 patients (52%) presented with arthralgia, 9 had clinical synovitis (16%) and DAS28-CRP of 3.7 (2.98-5.90). US sonography (34 patients) found at least one synovitis in 23 patients: 14 patients with grade 1 (66%), 6 patients grade 2 (29%), 1 patient grade 3 (5%), with a positive power Doppler signal in one case (3%). Among the patients having US-synovitis, 4 had clinical synovitis (17%), and 4 had X-ray erosions (17%). Radiological erosions were present in 8 patients (15%), without any correlation with clinical or US synovitis. Articular involvement (defined as clinical synovitis, US-synovitis and/or articular erosions) were found more frequently in limited SSc (n=28, 72%) than in diffuse SSc (n=4, 31%) ($p<0.001$), with a more frequent positivity of anti-centromere antibodies (n=23, 60% versus n=3, 20%). No correlation was found with disease severity or other organ impairment.

Conclusion

US synovitis were found more frequently than clinical synovitis, which are merely active, and do not correlated with articular destruction.

AUTO1-0289
THE ENIGMAS OF SYSTEMIC SCLEROSIS

AUTOANTIBODY PROFILING IN A LARGE DUTCH SYSTEMIC SCLEROSIS COHORT

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Background

Autoimmune antibody profiling plays a prominent role in both the classification of disease and establishing prognostic factors. Here we evaluated a well characterized Dutch clinical systemic sclerosis (SSc) cohort for the prevalence of autoantibody associated with SSc, and compared the results with a large Australian cohort.

Method

In total 353 patients (diffuse SSc (dcSSc), limited SSc (lcSSc) and SSc overlap syndrome), 21 disease controls and 50 healthy donors were included. Autoantibodies were measured in serum samples using line-immunoassay (LIA, Systemic Sclerosis Profile, Euroimmune).

Results

Autoantibodies	Dutch cohort %	Australian cohort %
Scl70	22	22
Centromere B	28	45
RNA polymerase III	6	16
Fibrillarine	2	1
Nor90	<1	4
Th/T0	1	3
Ku	1	3

Major findings are depicted in the table. Additionally, we investigated the autoantibodies anti-endothelin receptor-A and anti-angiotensin-II-receptor-I, known to be associated with

pulmonary arterial hypertension (PAH)[3]. Both these antibodies were present in some SSc patients, but also in healthy controls and did not show correlation with PAH. Of interest, we observed a high prevalence of autoantibodies associated with primary biliary cirrhosis, mainly for lcSSC patients (3.1% Sp100 and 6.5% M2-3E/M2), which could be indicative of higher risk to develop autoimmune liver disease.

Conclusion

This study reveals that patients can be divided into different subclusters based on autoantibody profiles. Clear differences were observed in frequency of centromere and RNA polymerase III autoantibodies between the Dutch and Australian cohort, possibly due to factors such as gender (percentage male 33% vs 12%), ethnicity (mainly Caucasian in Dutch cohort) or disease severity. Of course, behavioral and environmental determinants, which have not been studied in both the Australian and Dutch cohort, could be of influence. It is of interest to further evaluate these factors.

AUTO1-0945
THERAPEUTICALLY APPROACHES IN AUTOIMMUNE DISEASES

ANTI MDA5- A NOVEL AUTOANTIBODY THAT INDICATES SEVERE LIFE THREATENING INTERSTITIAL LUNG DISEASE IN PATIENTS WITH DERMATOMYOSITIS - A CASE REPORT

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Background

Anti-melanoma differentiation associated gene 5 (Anti-MDA5) dermatomyositis (DM) is a novel subtype of DM characterized by minimal muscle involvement, specific cutaneous manifestations and severe interstitial lung disease (ILD). Another finding is hyperferritinemia, a poor prognostic indicator. Anti-MDA5 is a new myositis specific autoantibody, originally known as CADM-140 since it was found in sera of clinically amyopathic dermatomyositis (CADM) patients with ILD, later, the identification of MDA5 as its autoantigen brought to its name as Anti-MDA5. This autoantibody frequently indicates a rapidly progressive ILD that is associated with high mortality rates.

Method

Case presentation: A 69-years-old Caucasian male was admitted to our hospital with a 3-week history of productive cough, dyspnea, arthralgia and myalgia. Physical examination revealed oral ulcers, heliotrope rash and bilateral crackles on lung auscultation. No signs of muscle weakness were observed. Laboratory findings included hypertriglyceridemia and ferritin level >2500 ng/ml, Anti-MDA5 test was positive. Chest Computed Tomography showed Ground Glass opacities in both lungs. Pulmonary function tests revealed a restrictive pattern. The diagnosis of Anti MDA5 associated CADM was established.

Results

The patient received glucocorticoids and one course of intravenous cyclophosphamide with a clinical improvement. However, his ferritin level remained elevated. The patient is designed for another course of Rituximab.

Conclusion

A clinician should bear in mind the diagnosis of Anti MDA5 when encountering a patient with typical symptoms since early treatment can improve prognosis. Nowadays, no standard therapy guidelines exist. Understanding the pathophysiology of the disease is crucial for decision making about appropriate treatment.

AUTO1-0181
THERAPUTICAL RESPONSE WITH ANTIBIOLOGICAL DRUGS ANTIBODIES

ADALIMUMAB THERAPEUTIC MONITORING IN AUTOIMMUNE DISEASE: COMPARISON OF THREE ELISA COMMERCIAL KITS

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Background

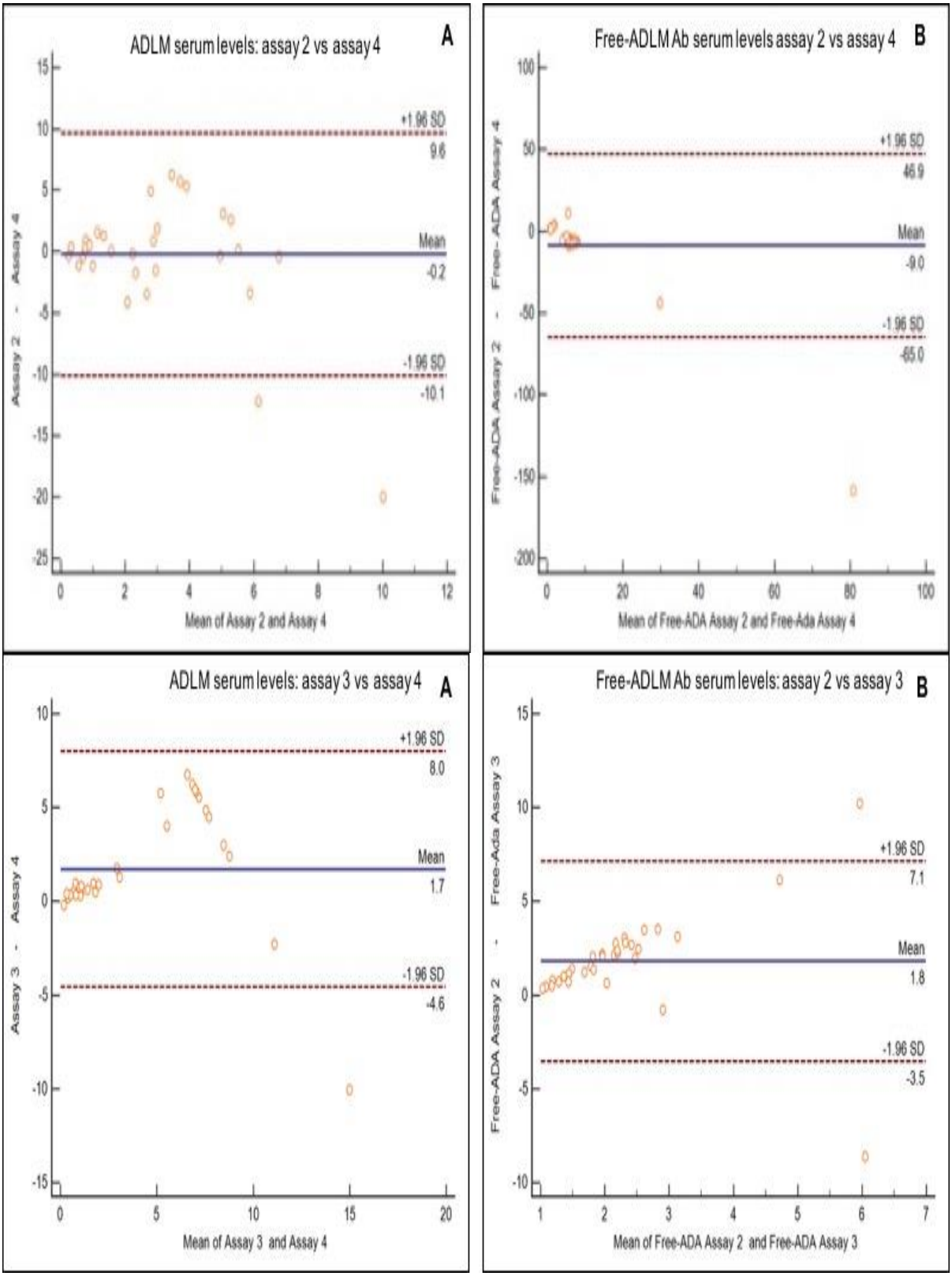
Autoimmune diseases treatment was revolutionized by the advent of biological therapy, however there is patients with loss of response because of the development of anti-drug antibodies (ADAb). ADAb can form immunocomplexes with the target drug influencing drug efficacy and pharmacokinetic. As to prevent these complications, the need of individualized treatment regime is becoming important and leads to design different Therapeutic Drug Monitoring (TDM) consisting in measuring of drug serum level and ADAb. Adalimumab (ADLM) is one of the most common biological drug used in the treatment of autoimmune diseases and in the last few years, different ELISA kits were developed for the detection of ADLM serum levels and anti-ADLM antibodies.

Method

We performed a comparison study of 3 different ELISA kits for ADLM monitoring therapy in patients with autoimmune disorders as to study the potential criticality and benefits. We analysed 32 patients affected by rheumatology, gastroenterology and dermatology diseases (4, 20 and 8 patients respectively) using Tani Medical®, Matrix® and Theradiag® commercial available kit. We performed the detection of ADLM serum levels and anti-ADLM antibodies and we compare these methods with Bland-Altman statistic test.

Results

Even if two methods are more concordant than other (figure 1), we found significant differences between assays both in serum ADLM level and in anti-ADLM antibodies (figure 2).



Conclusion

We want to underline the need of standardization and harmonization between different assay and we invite laboratory and physician to a tight collaboration designing specific TDM with using same ELISA assay in order to prevent potential laboratory mistakes.

AUTO1-0416
THERAPUTICAL RESPONSE WITH ANTIBIOLOGICAL DRUGS ANTIBODIES

CIRCULATING AUTOANTIBODIES FOR PREDICTION OF RESPONSE TO INFLIXIMAB IN RHEUMATOID ARTHRITIS

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Background

Approximately a third of Rheumatoid Arthritis (RA) patients treated with tumor necrosis factor (TNF)-α inhibitors such as Infliximab (IFX) fail to respond. This has prompted a widespread interest in the finding of predictors of response to TNFα inhibitors. Here, we aimed to search for serum autoantibodies that aid to identify RA patients most likely to benefit from IFX.

Method

We analyzed 170 individual sera collected at baseline from 3 independent sample sets (1 discovery set + 2 validation sets) consisting of biologic-naïve RA patients assigned to receive IFX plus methotrexate. European League Against Rheumatism (EULAR) criteria were used to assess the clinical response at six months of follow-up: good response (GR, n=60), moderate (MR, n=59) and non-response (NR, n=51). A suspension bead array platform built on protein fragments within Human Protein Atlas and selected from an initial screening using an array containing 42000 antigens was employed to identify the IgG and IgA autoantibodies in the discovery set and validate the results within the 2 validation sets.

Results

Our data revealed increased IgG autoantibody levels against the antigen Centromere Protein F (CENPF) in GR compared with NR. Our results also showed that IgA autoantibodies toward the antigen Zinc transporter ZIP2 (SLC39A2) were decreased in GR when compared with MR.

Conclusion

We have identified novel autoantibodies in RA that associate with IFX response, which could potentially be useful to guide the treatment decisions for IFX and lead to further studies focusing on the role of the autoantibodies against CENPF and SLC39A2 within RA.

AUTO1-0441
THERAPUTICAL RESPONSE WITH ANTIBIOLOGICAL DRUGS ANTIBODIES

COMPETITIVE ELISA FOR DETECTION OF NEUTRALIZING ANTI-DRUG ANTIBODIES EXHIBITS COMPARABLE RESULTS TO REPORTER GENE ASSAY

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Background

Reduced clinical response in patients treated with TNF-a inhibitors are influenced by their immunogenicity, formation of neutralizing and non-neutralizing antibodies. Different methods used for detection of anti-drug antibodies (bridging ELISA, Reporter Gene Assay (RGA) ...), differentiate in the reported levels and types of the detected antibodies.

The aims of this study were to:

-develop an *in-house* competitive ELISA (cELISA),

-analyze patient sera for anti-Infliximab and anti-Adalimumab levels with cELISA and

-compare results of cELISA with functional RGA.

Method

Serum samples of patients with chronic inflammatory bowel and rheumatic diseases treated with Infliximab or Adalimumab but with undetectable concentrations were tested for anti-Infliximab and anti-Adalimumab antibodies using cELISA and RGA (Fig1). In development of cELISA the cut-off, within and between-run imprecisions were evaluated.

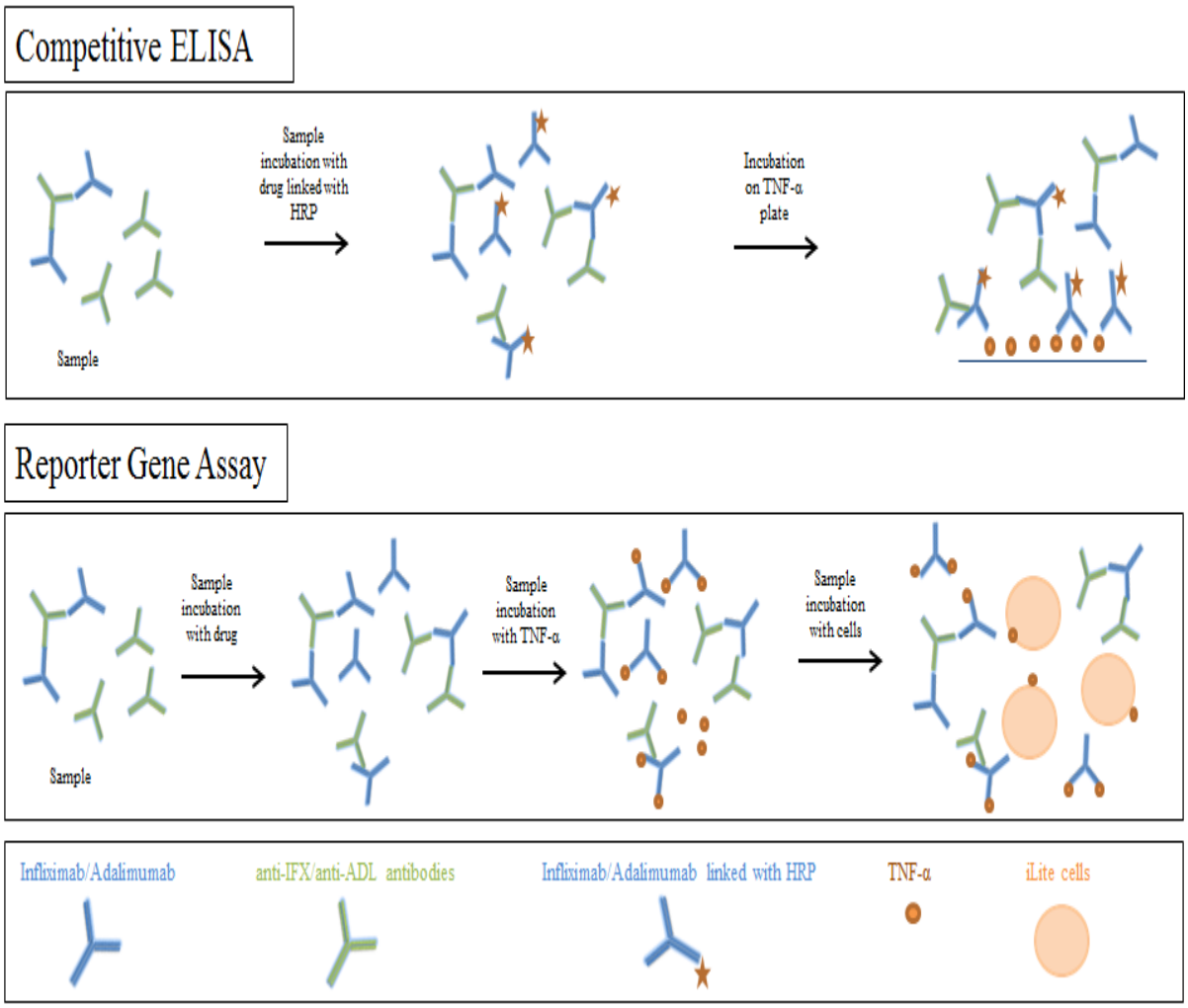

Fig1: Competitive ELISA and RGA methodologies

Results

Cut-off in cELISA was defined according to results of samples tested negative in RGA. Between- and within-run imprecisions were < 20%. The results of anti-Infliximab and anti-Adalimumab antibodies measured in 99 samples (Infliximab; n=56, Adalimumab; n=43) tested either with cELISA or RGA showed the 100% agreement. The anti-Infliximab antibodies were detected in 35 (63%) samples and anti-Adalimumab antibodies were detected in 20 (47%) samples with RGA and cELISA. A correlation of 0.933 ($p<0.0001$) was found between cELISA and RGA anti-Inliximab positive results and a correlation of 0.972 ($p<0.0001$) was found between cELISA and RGA anti-Adalimumab positive results.

Conclusion

A cELISA was developed to detect antibodies against Infliximab and Adalimumab comparable to RGA. This enables us to confirm functional and neutralizing anti-drug antibodies with a significant applicative advantage.

AUTO1-0341
THERAPUTICAL RESPONSE WITH ANTIBIOLOGICAL DRUGS ANTIBODIES

INFLIXIMAB LEVELS AND ANTI-DRUG ANTIBODIES IN PATIENTS WITH RHEUMATOID ARTHRITIS - TREATMENT RESPONSE AND DRUG SURVIVAL DURING FIRST YEAR

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Background

Even though most of patients with rheumatoid arthritis (RA) respond favorably to anti-TNF treatment, around 30% of patients have primary response failure or experience decreased treatment effect over time (secondary response failure). We aimed to analyse the clinical relevance of infliximab (IFX) concentration and the production of anti-drug antibodies (ADA) in patients with RA undergoing IFX treatment during the first treatment year.

Method

The drug levels and ADA were analyzed in relation to clinical disease activity as measured by disease activity score in 28 joints (DAS28), EULAR treatment response criteria, and drug survival.

Results

Blood samples were obtained at 4 months and at 1 year from 40 RA patients (80% females; mean age 55±12 and disease duration 11±12 years; mean DAS28 4.8±0.1; median methotrexate dose 20mg/week) refractory to previous immunomodulatory therapy and were treatment naïve for biologics. The drug survival on infliximab was 85% at 4 months and 53% at 1 year. At 4 months and 1 year, 43% respective 33% of patients had good EULAR treatment response with median IFX level 2.0, interquartiles 0.7-3.0µg/ml. EULAR moderate response was seen in 23% respective 8% of patients with sub-therapeutic IFX levels (1.6; 0.3-2.8 µg/ml and 1.3; 0.2-1.7 µg/ml, respectively). At 4 months, 20% of patients had no treatment response (median IFX level 0.3, IQR 0.2-3.0µg/ml). IFX concentration was undetectable in 6 patients all of whom presented high titres of ADA.

Conclusion

The formation of ADA during infliximab treatment is associated with loss of treatment response, the appearance of infusion reactions and discontinuation of treatment.

AUTO1-0768
THERAPUTICAL RESPONSE WITH ANTIBIOLOGICAL DRUGS ANTIBODIES

RESIDUAL SERUM RITUXIMAB LEVELS AND NEUTRALIZING ANTI-RITUXIMAB ANTIBODIES MAY PREDICT EARLY REMISSION AND RELAPSE IN PLA2R1-RELATED MEMBRANOUS NEPHROPATHY

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Background

Various Rituximab protocols can induce remission in membranous nephropathy (MN).

Method

We compared two regimens in 2 cohorts of anti-PLA2R1 positive MN patients: 23 patients from Nice were treated with two 1-g infusions at 2-week interval, and 27 patients from the GEM-Ritux trial received two 375 mg/m^2 infusions at 1-week interval. We measured serum rituximab levels and neutralizing anti-rituximab antibodies at months 3 (M3) and 6 (M6).

Results

Remissions occurred at M6 in 17 (73.9 %) Nice patients and 8 (29.6%) GEM-Ritux patients (p=0.0041), including 4 complete remissions vs none respectively. During follow-up, remission occured in 20 (86.9%) Nice patients and 18 (66.7%) GEM-Ritux patients (NS). The median time to remission was 3 and 9 months respectively (p=0.02). Patients treated with high-dose rituximab had higher serum rituximab levels at M3 (p<0.0001), lower CD19 count at M3 (p=0.0004) and M6 (0.0002), and less epitope spreading at M6 (p=0.0489). In the total study population, the variables at M3, associated with subsequent remissions at M6 and last follow-up were: higher rituximab levels (p=0.0013 and p=0.0452), lower CD19 counts (p=0.0030 and p=0.0314), lower PLA2R1 antibody titers (p=0.0212 and p=0.0002) and high-dose rituximab for patients with epitope spreading (p=0.0071 and p=0.0203, respectively). Neutralizing anti-rituximab antibodies were detected in 7 patients. Among the 38 patients who reached remission, 7 relapsed. Relapses were associated with neutralizing anti-rituximab antibodies at M6 (p=0.0133) and epitope spreading at diagnosis (p=0.0127).

Conclusion

In conclusion, remission depends on rituximab protocols and residual serum rituximab levels at M3. Neutralizing anti-rituximab antibodies at M6 may favor relapses.

AUTO1-0556
THERAPUTICAL RESPONSE WITH ANTIBIOLOGICAL DRUGS ANTIBODIES

AUTOANTIBODIES AS PREDICTORS OF RESPONSE TO THERAPY IN RHEUMATOID ARTHRITIS

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Background

Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are important diagnostic tools in rheumatoid arthritis (RA). Other antibodies such as anti-RA33 may be particularly helpful in RF/ACPA negative patients. These antibodies are predominantly of the IgM (RF) or IgG (ACPA, anti-RA33) isotype.

Method

To investigate the (i) diagnostic and (ii) potential prognostic value of other isotypes, sera from 292 RA patients, 261 disease controls and 100 healthy subjects were tested for the presence of RF, ACPA and anti-RA33 IgG/A/M isotypes by EliA™ (Thermo Fisher Scientific). For finding associations with American College of Rheumatology (ACR)20 therapeutic responses, an inception cohort of 165 RA patients was analysed.

Results

185 (63.4%) RA patients tested positive for at least one routine marker (IgM-RF or IgG-ACPA) while 107 were negative for both antibodies. Among these, 24 (8.2%) tested positive for IgG/A/M anti-RA33 and/or IgA-RF/ACPA. Diagnostic specificity of antibodies was at least 95%. To determine the prognostic value regarding therapeutic responses a cross-validated combined model with an accuracy of 77% and an estimated *p*-value (k=10) of 0.00034 showed high levels (>133 IU/ml) of IgM-RF to be associated with a favourable response to methotrexate (MTX). In case of low or no RF, the presence of IgG-RA33 antibody on the one hand, and the absence of IgA-ACPA on the other hand was associated with a favourable response.

Conclusion

Thus, these data suggest that determination of multiple antibodies increases the diagnostic power of serological testing and may be a feasible tool for the prediction of MTX response especially in combined models.

AUTO1-0848
VACCINE AND AUTOIMMUNITY, THE GOOD THE BAD AND THE UGLY

VACCINES AND NEUROINFLAMMATION

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Background

Post-vaccination adverse reactions are a reason of strong debate among scientists. Unfortunately, we often make the mistake of discussing just the epidemiology but not the molecular biology. The action mechanism of the vaccines is still not fully known despite the fact that aluminum adjuvants have been used for about 100 years.

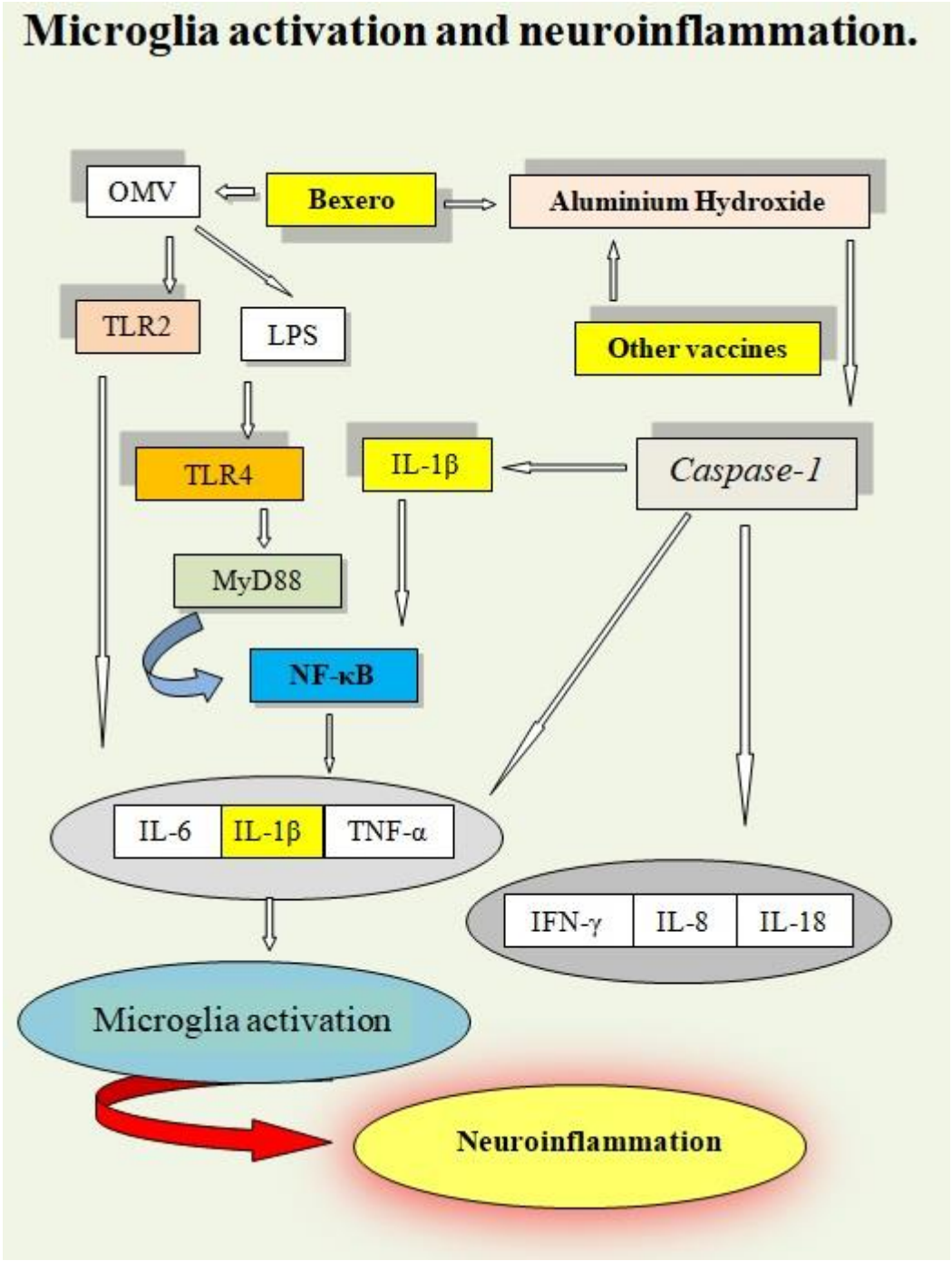
Method

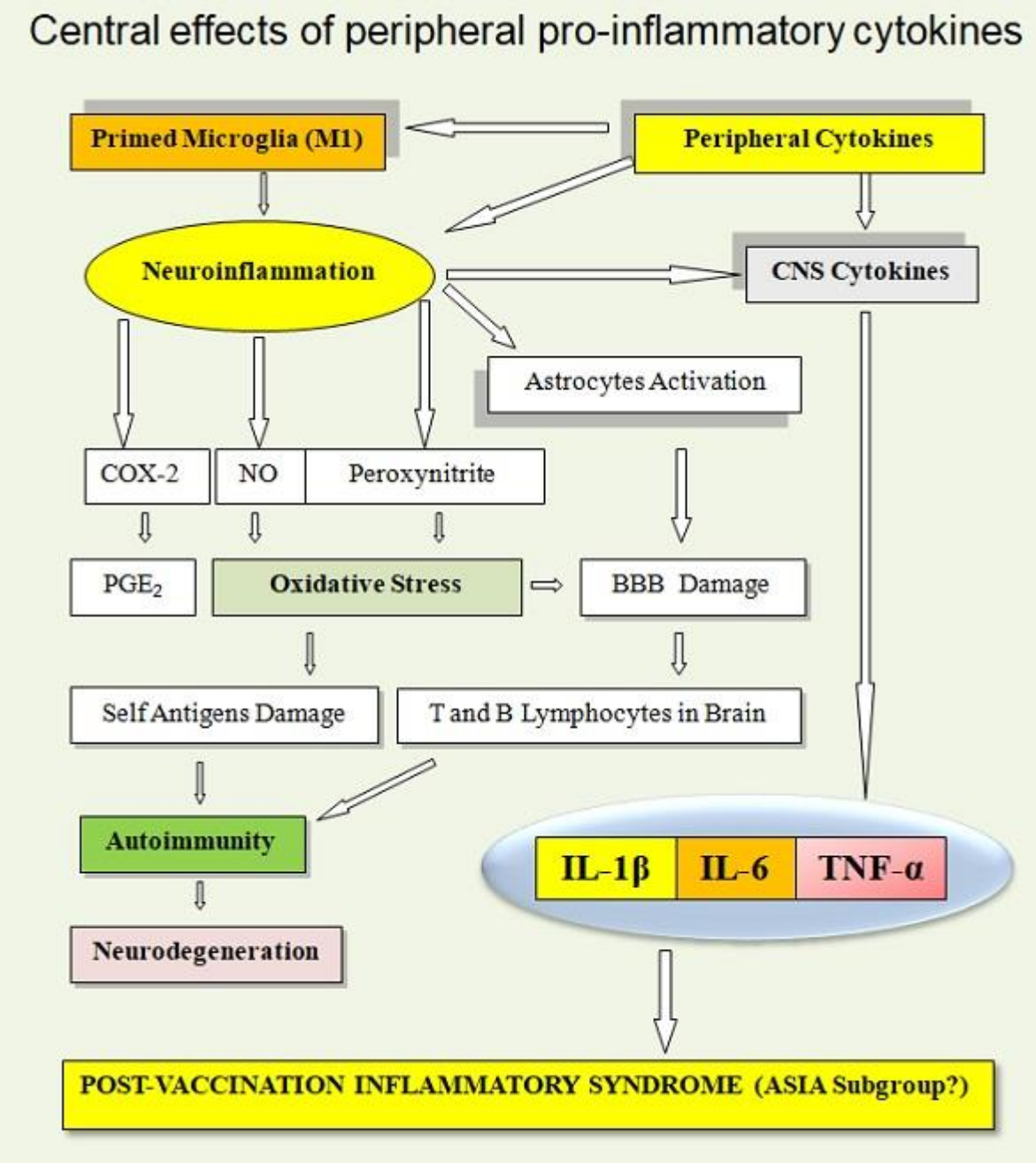
*

Results

Hypothesis:
We hypothesized a link between vaccinations and neuroinflammation. The peripheral pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), expressed after the injection of the vaccines containing aluminum adjuvants (Fig. 1), can reach the brain and cause neuroinflammation after microglia activation (Fig. 2). Elevated pro-inflammatory cytokines, particularly TNF-α, have been described in studies regarding the cytokines profile in autistic children. IL-1β represents a cytokine that controls the local pro-inflammatory cascade and thereby affects the balance between protective immunity and destructive inflammation. A subgroup of children with ASD have developed neuroinflammation. Several postmortem studies have confirmed the activation of microglia and neuroinflammation. A recent study has shown the presence of aluminum in the brains of individuals with autism and this aluminum was also found in microglia cells. Aluminum from vaccines is redistributed to numerous organs including brain, where it accumulates. Each vaccine adds to this tissue different level of aluminum. Aluminum, like mercury, activates microglia leading to chronic brain inflammation and neurotoxicity.

Microglia activation and neuroinflammation.





Conclusion

The peripheral pro-inflammatory cytokines, expressed after the injection of the vaccines containing aluminum adjuvants, can reach the brain and cause neuroinflammation after microglia activation. In some subjects with ASD there is neuroinflammation and aluminum accumulation in the brain.

AUTO1-0403
VACCINE AND AUTOIMMUNITY, THE GOOD THE BAD AND THE UGLY

PNEUMOCOCCAL DISEASE AND PNEUMOCOCCAL VACCINE IN PATIENTS WITH AUTOIMMUNE DISEASE

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Background

The incidence of Pneumococcal infection (PI) in patients with autoimmune disease (AD) is low.

Method

Objective: analyze prevalence of PI in patients with AD+ detect risk factors. Observational retrospective study in patients with AD, 2006-2017.

Results

331 patients were included, 272 (82.2%) woman, median age 59.1 (SD 15.4), 91(27.5%) smokers, 33 (10%) diabetes and 30 (9.1%) had previous neoplasm. AD were: RA 124 (37.5%), SLE 98 (30%), systemic sclerosis 57 (17.2%), ANCA vasculitis 27 (8.2%), GCA 8 (2.4%), Sjögren 7 (2.1%), rhupus 2 (0.6%), Takayasu arteritis 2 (0.6%), RA+Sjögren 5 (1.5%), SLE+Sjögren 1 (0.3%). 92 (27.8%) had active disease. 1 DMARD in 179 (54.1%) and 2 in 62 (18.7%). Most frequent drugs: metothrexate 85 (25.7%), azatioprine 26 (8.8%). Biologics in 86 (26%): tocilizumab 22 (6.7%), etanercept 15 (4.5%). 157 (47.4%) patients were vaccinated: CPV-13+PPV-23 in 76 (23%), PPV-23 in 62 (18.8%) and CPV-13 in 19 (5.7%). 8 (2.4%) PI were registered. 1 inferior respiratory tract infection diagnosed by urinary antigen and 7 pneumonia, 2 diagnosed by sputum and the rest by urinary antigen. 1 of them was considered an invasive PI because of the positivity of the blood cultures. All the patients received antibiotics and had a correct evolution, except by the patient with pneumococcal invasive infection, who died because of the infection. Median follow up was 3660.1 (SD2351.1) days. The patients with PI were older: [77.4 (SD 9.9) vs 58.7 (SD 15.2), p=0.0006].

Conclusion

Pneumococcal infection is not frequent in patients with AD, probably related with an almost 50% pneumococcal vaccination rate.

AUTO1-0206
VACCINE AND AUTOIMMUNITY, THE GOOD THE BAD AND THE UGLY

THE IMMUNOGENICITY OF SEASONAL AND PANDEMIC INFLUENZA VACCINATION IN AUTOIMMUNE INFLAMMATORY RHEUMATIC PATIENTS – A SIX MONTH FOLLOW UP PROSPECTIVE STUDY

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Background: Influenza can provoke severe complications and vaccination is recommended for autoimmune inflammatory rheumatic disease patients (AIRD). However, AIRD patients require cautious scrutiny in terms of immunogenicity, especially when taking immunomodulatory medications. Our aim was to determine the immunogenicity influenza vaccine in AIRD patients, its persistence, response to multiple vaccinations and the influence of different medications on patients' response.

Methods: 137 AIRD and 54 healthy controls (HC) were vaccinated with trivalent seasonal influenza. After 3-5 weeks 15 HC and 93 AIRD were vaccinated with pandemic influenza vaccine, 63 of patients were vaccinated a second time after 3-5 weeks. Sera were collected before vaccination, 18-90 days after each vaccination and more than 180 days after the last vaccination. The immune response was measured using haemagglutination inhibition (HAI) assay.

Results: After vaccination, geometric mean titres (GMT) of HAI, seroprotection and seroresponse were not compromised in AIRD, as compared to HC for all antigens. The elevation of HAI titer in medicated AIRD were higher than non-treated patients for all medications used, except rituximab. There was significant decrease in HAI GMT and seroresponse (Figure 1) at >180 days as compared to 18-90 days only in AIRD, but not in HC for all three seasonal influenza vaccine antigens. In pandemic influenza seroprotection increased 40% (from 37% to 77%) after the first vaccination, but only 7% (from 79% to 86%) after the second vaccination. There was 68% (13/19) of seroconversion observed after the first vaccination and 0% (0/3) after the second, while seroresponse was 52% (48/93) after first and 24% (14/58) after second vaccination. Also, second vaccination did not help to improve persistence of seroprotection or seroresponse.

Conclusion: Influenza vaccination is immunologically active for AIRD, with little value of the second dose of the pandemic vaccine. AIRD patients have lower persistence of seroresponse >180 days to antigens in seasonal influenza vaccine.

AUTO1-0062
VITAMIN D: TO D OR NOT TO D

MODULATORY EFFECTS OF VITAMIN D ON PERIPHERAL CELLULAR IMMUNITY IN PATIENTS WITH RECURRENT MISCARRIAGES

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Background

We aimed to investigate the modulatory effects of vitamin D on peripheral blood cellular immune response in patients with recurrent miscarriage (RM).

Method

Two hundred and thirty-three women with RM were included in the present study. Immunophenotype of peripheral blood lymphocytes, Th1 cytokines production (IFN-γ and TNF-α) and NK cytotoxicity were assessed during the middle luteal phase before any treatment by the flow cytometer. Forty RM women with low vitamin D level only received 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (calcitriol) supplementation for two months. The immunophenotype of peripheral blood lymphocytes, Th1 cytokines production and NK cytotoxicity were compred between the before treatment group and the after treatment group.

Results

The percentage of $CD19^+$ B cells and NK cytotoxicity at an effector to target cell (E:T) ratio of 50:1, 25:1 and 12.5:1 were significantly higher in the vitamin D insufficiency group (VDI) than in the vitamin D normal group (VDN) ($P < 0.05$ each). The proportion of TNF-α-expressing Th cells was significantly higher in the vitamin D deficiency group (VDD) and VDI than in VDN ($P < 0.05$). However, there were no significant differences in the proportion of IFN-γ-expressing Th cells among VDI, VDD and VDN. This dysregulation was significantly reduced with 1,25$(OH)_2$D supplementation.

Conclusion

The data suggest that the abnormalities of cellular immune response were observed in RM patients with a low vitamin D level, which could be regulated to some extent with 1,25$(OH)_2$D supplementation.

AUTO1-0570
VITAMIN D: TO D OR NOT TO D

EVALUATION OF RELATIONSHIP BEWTWEEN SERUM VITAMIN D LEVELS AND PERIPHERAL BLOOD NATURAL KILLER CELLS IN WOMEN WITH INFERTILITY

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Background

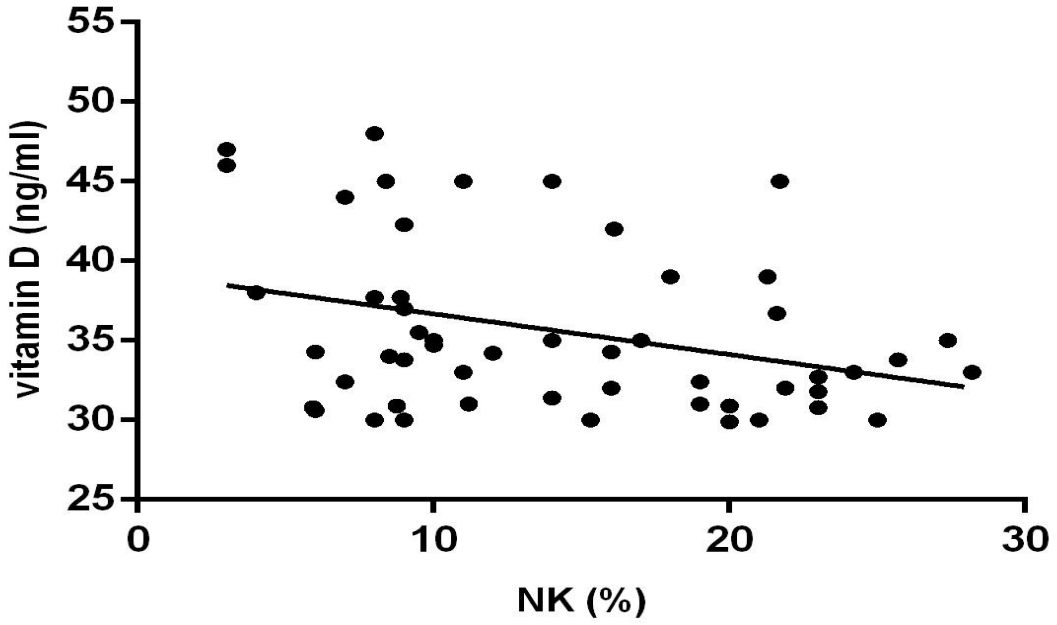
The influence of vitamin D on immuno-mediated conditions, including reproductive failure, may be linked to the presence of vitamin D receptors in immune cells. Increased Natural Killer (NK)-cell levels/cytotoxicity have been reported in women with primary infertility and recurrent spontaneous abortion (RSA). Vitamin D deficiency is a prevalent condition in women with infertility and RSA; however, the effect of vitamin D on NK cells is largely unknown.

Method

The present study seeks to determine the possible relationship between serum vitamin D content and peripheral blood NK in women with primary infertility and RSA. The study includes a cohort of 149 infertile women and 252 RSA women. Vitamin D status is graded as: normal status (>30 ng/mL), insufficiency (20-30 ng/mL) and deficiency (<20 ng/mL). Peripheral blood $CD56^{+}CD16^{+}$NK cells were evaluated by using flow-cytometry.

Results

Infertile and RSA women show similar levels of both vitamin D and NK cells. No difference in the prevalence of vitamin D deficiency results between infertile and RSA women. Moreover, no appreciable differences concerning NK levels occur in RSA and infertile women when they are stratified in accordance with vitamin D. An inverse correlation between vitamin D and NK results in the group of RSA women with a normal vitamin D status (P=0.017; Figure 1).



Conclusion

The effects of vitamin D on mature and developing NK cells are yet to be well determined. Our preliminary data suggest that vitamin D at higher levels may exhert a regulatory effect on NK cell number or distribution in infertile women.

AUTO1-0792
VITAMIN D: TO D OR NOT TO D

CRITICAL ASSESSMENT OF POTENTIAL GENETIC AND EPIGENETIC CONFOUNDERS IN THE RELATIONSHIP OF VITAMIN D AND AUTOIMMUNITY

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Background

Besides sustaining skeletal homeostasis, 1,25(OH)2 D3, is an immune modulator. D3's role in innate immunity is via antimicrobial peptides secretion, modulation of IL-1β, and IL-6. In adaptive immunity, D3 enhances the expression tolerogenic immune cells and cytokines (IL-10); inhibits memory B cell development and immunoglobulin productions. Together, these indicate the anti-inflammatory role of D3 and potential benefits related to inflammatory diseases including autoimmunity.

Method

However, unlike animal studies, human trial results are equivocal. We suspect unrecognized confounding may be involved. We postulate the following factors are the potential confounders.

Results

Smoking: Smoking is a major risk factor for autoimmune diseases. Moreover, lung has been known as an immunological staging ground[1] and smokers' lung may supply auto-reactive immune cells. Additionally, smoking causes CYP24A1 and CYP27B1 polymorphism that controls D3 activation and GATA3, a gene essential to Th2-programming transcription.[2] GATA3 deficient mice develop parathyroid abnormalities which directly affect Ca++ and D3 levels[3]. Th2 cytokine IL-4 has shown to enhance vitamin D catabolism in a CYP24A1 dependent manner.[4]

Diabetes and kidney disease: D3 may be involved in insulin secretion, beta cell survival, and calcium flux within beta cells. Additionally, D3 must be hydroxylated in the liver and kidney to be bioactive. Thus, diabetic or kidney disease patients will have insufficient serum D3 levels. Thus, D3, Calcium or parathyroid hormone are all linked to this relationship.

Genetic polymorphism: many immune-mediated diseases share several genetic loci[5]. Genetic polymorphism induced insufficient D3 levels [6-10] and 17 genes related to D3 also control immune function and DNA repair.**Conclusion**

AUTO1-1074
VITAMIN D: TO D OR NOT TO D

VITAMIN D - WHY DOES IT 'WORK' SO WELL?

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A decade ago I wrote that the various forms of Vitamin D were not 'vitamins', but a secosteroid hormone and its precursors. I showed how every human cell makes the 'Vitamin D' it needs to transcribe genes without any of the precursors being present in the diet. Nobody has refuted my analysis, yet Medicine seems to have paid little attention.

There is still active debate over whether I was correct in warning about long-term deleterious actions of 'Vitamin D' in the human body. The consensus in the short-term is quite clear - most people find that taking high-dose 'Vitamin D' (the steroid precursor) makes them feel better.

I do not disagree, indeed, there is a good reason why 'Vitamin D' 'works' so well in the short-term, 1-10 years, timeframe. That reason is embodied in the statistic that 60% of US adults are taking a drug for at least one diagnosed chronic disease, and that 12.5% have 5 or more diagnoses. Any drug which modulates the symptoms of chronic disease is therefore going to affect a very large proportion of the population, and the Vitamin D precursors do just that. Supplementing with a precursor suppresses the patient's innate immune response - just as cortisone or prednisone would do, but less aggressively, with fewer short-term side-effects.

For nearly 16 years I have been observing a cohort of hundreds of elderly folk with chronic immune diseases who have chosen to avoid dietary sources of 'vitamin-D.' Their measured blood 25-D levels are routinely below 12ng/ml, below the level usually considered 'severely deficient'. Why hasn't this made their bones weak, and their chronic condition worse?

Is it perhaps because every human cell makes all the active Vitamin D it needs to transcribe DNA without any of the precursors being present in the diet, just as we have described?

We will revisit how the vitamins-D affect the human body, and discuss some of the options available to help mitigate chronic symptom surges

AUTO1-0420
VITAMIN D: TO D OR NOT TO D

GENE EXPRESSION PROFILE OF TOLEROGENIC DENDRITIC CELLS DIFFERENTIATED WITH VITAMIN D3, DEXAMETHASONE AND RAPAMYCIN

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Background

Tolerogenic dendritic cell (tolDC)-based therapies have become promising approaches for the treatment of autoimmune diseases by their potential ability to restore immune tolerance in an antigen-specific manner. There is a broad variety of protocols to generate tolDC *in vitro*, being their differentiation in the presence of vitamin D3 (vitD3-tolDC), dexamethasone (dexa-tolDC) or rapamycin (rapa-tolDC) three of the most frequent. However, the characteristics of these cells are very heterogeneous, thus making the need to find common genetic pathways and biomarkers of high relevance. Therefore, the objective is to compare the transcriptomic profile of vitD3-tolDC, dexa-tolDC and rapa-tolDC in order to find them.

Method

Monocyte-derived dendritic cell differentiations of immature (iDC), mature (mDC), vitD3-tolDC, dexa-tolDC and rapa-tolDC from 5 healthy donors were generated, and a microarray analysis was performed (Affymetrix). Results were normalized and filtered, and differentially expressed genes (DEG) were selected. A Gene Set Enrichment Analysis (GSEA) was performed to select common enriched pathways. Statistical analyses were performed using R software.

Results

Common DEG could not be found for the three tolDC protocols, although 14 genes (many of them immune-related) appeared up-regulated in at least one condition. GSEA revealed 11 common protein sets differentially expressed in tolDC. However, all of them were induced for vitD3-tolDC and dexa-tolDC, while down-regulated in rapa-tolDC.

Conclusion

The analysis revealed that, despite not sharing potential common biomarkers, vitD3-tolDC and dexa-tolDC presented similar transcriptomic profiles, suggesting an induction of immune tolerance through common pathways, while rapa-tolDC seem to develop their function through different ones.

AUTO1-0412
VITAMIN D: TO D OR NOT TO D

VITAMIN D SUPPLEMENTATION AND DISEASE ACTIVITY IN PATIENTS WITH IMMUNE-MEDIATED RHEUMATIC DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background

Vitamin D serum levels and the presence and activity of rheumatic conditions have been associated. However, many studies are merely observational, and the existent randomized clinical trials were never systematically analyzed. Therefore, this study aims to provide a systematic review and meta-analysis of such a topic.

Method

MEDLINE, EMBASE, LILACS, COCHRANE, and CINAHL were explored to identify randomized trials that investigated clinical repercussions of vitamin D (or analogs) supplementation for at least 3 months in rheumatic diseases. Standardized clinical and/or laboratorial outcomes related to disease activity were analyzed according to each disease before and after supplementation.

Results

Database searches rendered 668 results; 9 were included-5 on rheumatoid arthritis, 3 on systemic lupus erythematosus, and 1 on systemic sclerosis. Seven of the studies were meta-analyzed. After vitamin D supplementation, rheumatoid arthritis recurrence decreased; however, not significantly (risk difference=-0.10, 95% CI=-0.21, 0.00, P=.05). No statistical significance was observed regarding visual analog scale (mean difference=2.79, 95% CI=-1.87, 7.44, P=.24) and disease activity score28 (mean difference=-0.31, 95% CI=-0.86, 0.25, P=.28). Regarding systemic lupus erythematosus, anti-dsDNA positivity was significantly reduced (risk difference=-0.10, 95% CI=-0.18, -0.03; P=.005).

Conclusion

Vitamin D supplementation reduced anti-dsDNA positivity on systemic lupus erythematosus and could possibly reduce rheumatoid arthritis recurrence, although novel randomized clinical trials are needed to confirm and extend the benefits of this hormone in immune-mediated rheumatic diseases.

AUTO1-1086
VITAMIN D: TO D OR NOT TO D

VITAMIN D SUPPLEMENTATION DILEMMA; MINIMUM, MAXIMUM, OPTIMUM

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During the past two-decades extended research carried out in spectrum of medical sciences revealed pleiotropic vitamin D actions that regulate calcium and phosphate absorption as well as the metabolism of organs, tissues and cells in human body. The optimal serum 25-hydroxyvitamin D [25(OH)D] concentrations were associated with improved clinical outcomes for several chronic, communicable and non-communicable diseases. As a result, medical scientific organizations developed guidelines for vitamin D supplementation to obtain and maintain optimal serum 25(OH)D concentrations both in general populations and risk groups. However, available guidelines differ significantly depending on the perspective on human health. The bone-centric guidelines recommend a target 25(OH)D concentration of >20 ng/mL (>50 nmol/L), and age-dependent daily vitamin D doses of 400-800 IU. The pleiotropic-centric guidelines recommend a target 25(OH)D concentration of >30 ng/mL (>75 nmol/L), and age-, body weight-, disease-status, and ethnicity dependent vitamin D doses ranging between 400-4000 IU/day. The guidelines to follow must depend on one's individual health outcome concerns, age, body weight, latitude of residence, insolation, dietary and cultural habits. Therefore, the regional or nationwide pleiotropic-centric guidelines appear more applicable in clinical practice, including the prophylactic and treatment regime of autoimmune disorders. The natural sources (sun, diet) are regarded ineffective to maintain the year-round 25(OH)D concentrations in the range of 30-50 ng/mL (75-125 nmol/L) in the general population. In consequence, vitamin D deficiency is highly prevalent irrespective of age and the most effective method to obtain and maintain proper vitamin D status and possible health benefits related to vitamin D is the regular supplementation of vitamin D with use of recommended daily vitamin D doses.

AUTO1-0635
PLENARY 2

REGULATORY CHECKPOINTS CONTROLLING THE TRANSITION BETWEEN AUTOIMMUNITY AND INFLAMMATION (1st Prize Winner)

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During inflammation and infection, we are simultaneously confronted with both self and non-self in form of dying cells and microbes, respectively. Mechanisms that facilitate the non-immunogenic clearance of self-antigens derived from apoptotic and necrotic cells and that, in parallel, allow the initiation of an immune response against invading pathogens are incompletely understood. Recent data from our laboratory show that the immune system actively sorts apoptotic cells (ACs) and bacteria into distinct subspecies of phagocytes thereby enabling a segregated processing of self and non-self as well as a differential immune response against these two entities. During inflammation, ACs were cleared by tissue resident macrophages (resMφ) that performed a non-immunogenic disposal of self antigens, whereas bacteria were preferentially ingested by monocyte-derived inflammatory macrophages. We identified the enzyme 12/15-lipoxygenase and the nuclear receptor Nr4a1, both specifically expressed by resMφ, as key factors that control the coordinated and non-immunogenic phagocytosis of ACs by these specialized macrophage subset. Incorrect sorting and aberrant uptake of AC-derived self-antigens by pro-inflammatory and immunocompetent phagocytes, however, resulted in the break of self-tolerance and autoimmunity. Our data thus demonstrate the importance of a sorted clearance of ACs for the maintenance of immunologic self-tolerance during inflammation.

AUTO1-0821
PLENARY 3

HELMINTHES AND AUTOIMMUNITY; A LOVE STORY (AESKU PRIZE FOR LIFE TIME CONTRIBUTION)

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In Western countries, a strong reverse correlation exists between improved sanitation/hygiene and high prevalence of parasitic worms (helminthes) in certain geographic areas, leading to autoimmune diseases. Hence, there is a significant increase in the prevalence in autoimmune diseases. The aim of the helminthes is to protect themselves via immunomodulation of the host Immune network. The immunoregulatory functions of some helminths were attributed to the phosphorylcholine (PC) moiety on the helminthes' secretory molecules. We have constructed a bi-spcific molecule PC-tuftsin (TPC), and analyzed the immunomodulatory activity in autoimmune murine models and the mechanism of action.

Our data show attenuation the clinical score of murine autoimmune models|: lupus in NZBxW/F1 mice, collagen induced arthritis and DSS induced colitis. In all the three autoimmune conditions, TPC decreased the secretion of pro-inflammatory cytokines (TNFα, IL-1β, IL-6,IFNγ) and enhanced production of anti-inflammatory IL-10; elevated the expansion of T regulatory cells and B regulatory cells.

The immunomodulatory activity of TPC was attributed to its bi-specific activity: a) The tuftsin part of the TPC shifts raw macrophage cells from pro-inflammatory macrophages M1 to anti-inflammatory M2-secreting IL-10 ($p<0.001$), and Tregs, through the neuropilin-1. b) TPC inhibited significantly TLR4 expression by HEKTM-mTLR4 cells, leading to inhibition of NFkB expression ($p<0.02$), via the phosphorylcholine end of the molecule. The detailed mechanism of activity will be discussed.
Our data propose a potential small molecule to treat autoimmune state.

AUTO1-0789
PLENARY 4

HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS: A CLASSIC IMMUNE COMPLEX DISEASE

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There is increasing awareness of the link between inflammation, autoimmunity, and atherothrombosis in stroke and myocardial infarction and the need for non-anticoagulant management of autoimmune thrombotic disorders, such as systemic lupus, anti-phospholipid syndrome, autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia. Our data implicate neutrophil (PMN)-derived α-defensins (α-defs) in the pathogenesis of atherothrombosis. α-defs are a family of four small cationic, hydrophobic, highly disulfide linked antimicrobial peptides that are the predominant proteins by mass released from the azurophilic granules of activated human PMNs. Plasma levels of α-defs rise from the nM to the μM range in patients with serious immune and infectious disorders and much higher concentrations likely accrue at the interface between degranulating PMNs and inflamed host tissue. The potential role of α-defs in atherothrombosis has been overlooked in part because these peptides are not expressed in murine PMNs.

In previous studies, we have shown that α-defs promote fibrin formation, inhibit tPA-mediated endothelial fibrinolysis, inhibit degradation of LDL, promote irreversible binding of Lp(a) to vascular matrices and inhibit ADAMTS13 (the enzyme involved in TTP) in vitro. More recently, we have characterized the pathobiology of these peptides in a transgenic mouse that expresses α-def-1 (the predominant peptide species) in its PMNs (hereafter Def++). Def++ mice develop acute capillary leak, neutrophil extravasation, extravascular deposition of fibrin and severe acute lung injury following mild inhalation challenge, effects mediated through the low-density lipoprotein-related receptor. Def++ mice also develop a novel species of LDL/α-def-1 particles that bind more avidly than normal to the endothelium, generate endothelial- and monocyte-cathepsins, accelerate transcellular migration of LDL into the matrix and cause lipid accumulation in the aorta even while mice are ingesting a regular chow diet and have normal/subnormal levels of plasma LDL. Lastly, Def++ mice are highly prothrombotic. Partial mechanical obstruction of the inferior vena cava activates the intrinsic pathway of coagulation, generating kallekrein, which activates PMNs to release α-defs that incorporate into fibrin and generate clots that are resistant to heparin and are 10x larger than those seen in syngeneic wild type mice. Importantly, oral or intravenous colchicine, a drug used safely for decades to treat inflammatory disorders, prevents release of α-defs, prevents thrombosis, restores responsiveness to heparin without enhancing bleeding, and inhibits development of lipid streaks in the aortas in mice on a normal chow diet.

Together, these studies suggest that antimicrobial α-defs released from PMNs during an innate or adaptive immune response damage host tissue, alter lipoprotein metabolism and promote thrombosis. Inhibition of neutrophil degranulation may provide a clinically useful means to prevent and mitigate the complications of atherothrombosis.

AUTO1-0020
PLENARY 4

VIRUSES AND HUMANS: A LONG EVOLUTIONARY PATH TOWARDS SELF-IMMUNITY; MOLECULAR MIMICRY AS A CURTAIL FACTOR IN AUTOIMMUNITY

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Although separated by hundreds of millions of years of evolution, viruses and humans share patterns of peptide expression that are against any expectations from a probabilistic viewpoint. Such a peptide commonality indicates a strict relationship between viruses and the origin of eukaryotic cells. Indeed, according to the viral eukaryogenesis hypothesis and in the scenario outlined by the endosymbiotic theory, the first eukaryotic cell (our lineage) originated around 1.6 billion years ago as a consortium consisting of a viral ancestor of the nucleus, an archaeal ancestor of the eukaryotic cytoplasm, and a bacterial ancestor of the mitochondria. Therefore, it seems that, more than a relationship, there is a strict kinship between viruses and humans. This might cast a shadow on the current immunization practices. In fact, the massive viral vs human peptide overlap could underlie a direct causal association between immune recognition of common sequences (that is, crossreactivity) and the current uncontrolled, unrestrained, pandemic tide of autoimmune diseases worldwide. The logically obliged conclusion is that only immunizations based on peptide fragments unique to infectious agents are expected to specifically hit the pathogens without the risk of harmful autoimmune crossreactivity with proteins of the human host.

AUTO1-1045
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

A SERUM NUCLEAR MAGNETIC RESONANCE-BASED METABOLOMIC SIGNATURE OF ANTIPHOSPHOLIPID SYNDROME

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Background

Antiphospholipid syndrome (APS) is a rheumatic inflammatory chronic autoimmune disease inducing hypercoagulable state associated with vascular thrombosis and pregnancy loss in women. Cardiac, cerebral and vascular strokes in these patients are responsible for reduction in life expectancy. Timely diagnosis and accurate monitoring of disease is decisive to improve the accuracy of therapy.

Method

In the present work, we present a NMR-based metabolomic study of blood sera of APS patients.

Results

Our data show that individuals suffering APS have a characteristic metabolomic profile of APS patients, with metabolite abnormalities associated to the metabolism of methyl group donors, ketone bodies and amino-acids.

Conclusion

We identify the first metabolomic fingerprint useful for APS stratification, having potential application to improve APS timely diagnosis and appropriate therapeutic approaches.

AUTO1-0822
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

A RARE CASE OF PLEURAL EFFUSION

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Background

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by recurrent arterial/venous thrombosis and/or gestational morbidity, thrombocytopenia and the presence of autoantibodies. Pulmonary thromboembolism (TE) and pulmonary hypertension are known complications of APS, however pleural effusion (PE) is extremely rare.

Method

We present a case of an unilateral PE associated with APS

Results

A 43-year-old caucasian woman who presented to the emergency department with a right back pain extended to the right hypochondrium, on the suspicion of acute cholecystitis an Abdominal CT was requested showing discrete bilateral PE. It is a patient with a history of thrombocytopenia with dyspnea and right thoracalgia, with no other known symptomatology. At the physical examination, the patient was eupneic with a decrease of the vesicular murmur on the right with softness. Analytically, there was elevation of inflammatory parameters and thrombocytopenia, with no other radiological alterations besides PE. The patient was hospitalized for study. The results of the thorococentesis showed an hematic exudate, non-infectious and non-neoplastic cell fluid. During the hospitalization the patient suffered a sudden episode of dyspnea with lipothymia and persistence of thoracalgia. Performed a thoracic CT angiography, which demonstrated bilateral TE and a right PE and analytically aggravation of thrombocytopenia. It was initiated therapy with Enoxaparin and three pulses of methylprednisolone with clinical, analytical and radiological improvement. The study of autoimmunity was requested concomitantly, obtained a positivity of Lupus anticoagulant (LA) and anti-Nuclear Antibody negativity as well as the other autoantibodies.

Conclusion

This case report represents a rare case of the association of PE with APS

AUTO1-0519
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

PREVALENCE OF ANTIPHOSPHOLIPID ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Anti-phospholipid antibodies are among the most frequent autoantibodies in SLE which includes anti-cardiolipin, anti-β2-glycoprotein I and lupus anticoagulant.We proposed to study prevalence of APL in Tunisian SLE patients.

Method

We retrospectively reviewed through a multicentric study 380 patients admitted from 1997 to 2016. All fulfilled the 1997 revised ACR criteria of SLE. Antiphospholipid syndrome is obtained when SAPL criteria were defined.

Results

We found 103 (39.6%) patients with APL among 380 patients with SLE included . 91 female and 12 male were registred. The mean age was 37.8 years. APL were anti-cardiolipin in 31.1%, anti-β2-glycoprotein I in 28.9% and lupus anticoagulant in 15.5%. SAPL syndrome is defined on 21.4% patients. Systemic manifestations were hematologic (91.3%) rheumatologic (86.4%) and dermatologic (83.5%).Vascular manifestations noted on 15.5% cases included arterial thrombosis (n=3), deep veinous thrombosis (n=6), myocardial infarction (n=1) and stroke (n=4). Study of clinical correlation showed association of anti-cardiolipin with valvular heart disease (p=0.047) and third class of lupus nephritis (p=0.009). Anti β2-glycoprotein I were associated with livedo (p=0.009) and lupus anticoagulant was associated with thrombosis (p=0.018).

Conclusion

APL are positive in 30–40% of SLE patients, as we found, but only 1/3 of them develop SAPL, while we registred only in 20 %. APL were associated with dermatologic, cardial and renal manifestations.The lupus anticoagulant is most strongly associated with venous and arterial thrombosis.

AUTO1-0620
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

A RARE CASEREPORT

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Background

Antiphospolipid

Method

elisa

Results

polyspecific

Conclusion

polyspecific

AUTO1-1049
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

SERONEGATIVE ANTIPHOSPHOLIPID SYNDROME IN RECURRENT REPRODUCTIVE FAILURE PATIENTS: ARE THE IGA ANTIPHOSPHOLIPID ANTIBODIES OUR NEW ALLIES?

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Background

IgA antiphospholipid antibodies (aPL) are not currently included in the criteria for the Antiphospholipid Syndrome (APS) classification. Several studies have pointed out the potential role of IgA-aPL in the pathophysiology of APS (thrombocytopenia, thrombosis), especially on seronegative and SLE patients. This role has also been reported in pregnancy morbidity.

Method

Fifty-nine patients, mean age 36.25±4.42 (recurrent miscarriage n=44, 74.58%; foetal death, n=9, 15.25%; recurrent implantation failure n=14, 23.73%) and 30 healthy controls, mean age 32.2±4.49 (with proven fertility) were tested for IgA, IgG and IgM anti-cardiolipin and anti-β2glycoprotein-I (Bioplex® 2200, Bio-Rad). We have also evaluated thrombocytopenia and prothrombotic markers (elevated D-dimer and activated partial thromboplastin time).

Results

Global incidence of IgA-aPL in our cohort was low (n=3, 5,36%). 12 out of 59 patients have IgG or IgM-aPL positive (21.43%). Only 2 were positive for IgA-aPL (3.57%), while one had only IgA positive aPL without IgG or IgM (1.79%). We observed a strong correlation between β2GPI-IgA with β2GPI-IgG (0,91), ACA-IgG (0,91) and with ACA-IgA (0,95). The correlation was low between β2GPI-IgA with ACA-IgM (0,19) and β2GPI-IgM (0,23).

Conclusion

In our cohort of 59 RRF patients, IgA-aPL helped to discriminate 3.57% of seronegative APS patients, which has relevant clinical implications. A strong correlation between IgA and IgG-aPL antibodies was observed. We suggest further investigation using a bigger RRF cohort according to classical aPL to warrant these observations.

AUTO1-1040
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

IMPACT OF ANTIPHOSPHOLIPID ANTIBODIES ON CLINICAL MANIFESTATIONS AND CARDIOVASCULAR RISK IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thrombosis and/or obstetric morbidity in the presence of antiphospholipid antibodies (aPL): lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL) and anti-β2 glycoprotein I antibodies (anti-β2-GPI), according to the Sydney criteria. The objective of this study was to evaluate the existence of associations between different aPL and age, gender, clinical manifestations, presence of another autoimmune disorder and cardiovascular risk factors (CRF) in patients with APS.

Method

A retrospective study of 35 patients with APS followed in a Portuguese central hospital was performed. The study evaluated the following variables: aPL profile, age, gender, clinical manifestations, type of thrombotic event, presence of another autoimmune disorder, CRF, Framingham risk score (FRS) and Systematic Coronary Risk Evaluation (SCORE).

Results

Current age: 51.03 ± 15.99 years	Obstetric morbidity: 17.14%
Follow-up time: 6.74 ± 4.67 years	Lupus anticoagulant: 70.59%
Women: 71.43%	Anticardiolipin antibodies 74.29%
Another autoimmune disorder: 25.71%	IgG 34.29%
Vascular thrombosis: 91.43%	IgM 40.00%
Only arterial thrombosis: 40.00%	Anti-β2 glycoprotein I antibodies 45.71%
Only venous thrombosis: 40.00%	IgG 37.14%
Arterial and venous thrombosis: 11.43%	IgM 17.14%
Thrombosis territory:	Diabetes mellitus: 5.71%
Cerebral: 42.86%	Arterial hypertension: 48.57%
Cardiac: 2.86%	Obesity: 40.00%
Pulmonary: 2.86%	Cigarette smokers: 11.43%
Renal: 2.86%	Total cholesterol: 148.00 ± 31.28 mg/dL
Suprarenal: 2.86%	Low-density lipoprotein: 91.84 ± 25.40 mg/dL
Intestinal: 2.86%	High-density lipoprotein: 53.39 ± 15.65 mg/dL
Splenic: 2.86%	Triglycerides: 101.02 ± 46.38 mg/dL
Upper limbs: 5.71%	FRS: 4.36%
Lower limbs: 42.86%	SCORE: 1.06%

Table 1 - Sample characteristics.

LA presence was more often in patients who had a stroke as a clinical manifestation of APS (p=0.010) and less often in patients with deep vein thrombosis (p=0.024). aCL

antibodies were associated with primary APS (p=0.030) and IgG aCL was associated with lower high-density lipoprotein levels (p=0.025). Anti-β2-GPI antibodies were associated with arterial thrombosis (p=0.010) and higher FRS (p=0.037) and IgM anti-β2-GPI was more frequent in older (p=0.001) and hypertensive patients (p=0.018).

Conclusion

In our study sample, different aPL profiles are associated with different manifestations and phenotypes of APS patients. Knowing these associations can be useful to predict new events and to reinforce the CRF control. A larger study sample is necessary to identify whether there are in fact APS phenotypes.

AUTO1-1053
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

IMPACT OF CLASSICAL CARDIOVASCULAR DISEASE RISK FACTORS ON CLINICAL MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME

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Background

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous and/or arterial thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies. APS has been associated with early atherosclerosis, coronary events and increased cardiovascular mortality. The objective of this study was to evaluate the cardiovascular and thrombotic risk of APS patients with different clinical manifestations.

Method A retrospective study of 35 patients with APS followed in a Portuguese central hospital was performed. The following variables were evaluated: clinical manifestations, type of thrombotic event, diabetes mellitus (DM), arterial hypertension (AHT), obesity, dyslipidemia, smoking, Framingham risk score (FRS), Systematic Coronary Risk Evaluation (SCORE) and the adjusted Global Antiphospholipid Syndrome Score (aGAPSS).

Results

Current age: 51.03 ±15.99 years	Splenic: 2.86%
Follow-up time: 6.74 ± 4.67 years	Upper limbs: 5.71%
Women: 71.43%	Lower limbs: 42.86%
Another autoimmune disorder: 25.71%	Obstetric morbidity: 17.14%
Vascular thrombosis: 91.43%	Diabetes mellitus: 5.71%
Only arterial thrombosis: 40.00%	Arterial hypertension: 48.57%
Only venous thrombosis: 40.00%	Obesity: 40.00%
Arterial and venous thrombosis: 11.43%	Cigarette smokers: 11.43%
Thrombosis territory:	Total cholesterol: 148.00 ± 31.28 mg/dL
Cerebral: 42.86%	Low-density lipoprotein: 91.84 ± 25.40 mg/dL
Cardiac: 2.86%	High-density lipoprotein: 53.39 ± 15.65 mg/dL
Pulmonary: 2.86%	Triglycerides: 101.02 ± 46.38 mg / dL
Renal: 2.86%	FRS: 4.36%
Suprarenal: 2.86%	SCORE: 1.06%
Intestinal: 2.86%	aGAPSS: 8.3 ± 4.06

Table 1 - Sample characteristics.

Patients with arterial thrombosis (AT) had a higher prevalence of AHT (p=0.028). Total cholesterol (TC) was lower in patients who had a stroke as a clinical manifestation of APS (p=0.032). All these patients were treated with statins. High-density lipoprotein (HDL) was lower in patients with AT (p=0.009) and higher in the group with deep vein thrombosis (p=0.045). Triglycerides were higher in patients who had non-obstetric thrombosis (p=0.028). FRS was higher in patients with AT (p=0.019). DM, obesity, smoking, low-density lipoprotein, SCORE and aGAPSS values were not statistically different among the subgroups with different manifestations.

Conclusion

Although there are several studies on this topic, they show divergent results. Some of our results are in line with the most recent literature, but larger studies are needed. We advise the research of these risk factors and their control to prevent new events.

AUTO1-0483
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

FREQUENCY OF MONOCLONAL GAMMOPATHY M IN SERA OF PATIENTS WITH ANTICARDIOLIPINE/B2gp1 IgM ANTIBODIES V. FERRE, G.MAKKI, G.DAMERON, N.BELMONTE, S.CAILLAT ZUCKMAN, D.BENGOUFA

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Background

Background: Monoclonal gammopathy of undetermined significance (MGUS) has been associated with an increased risk of thrombosis, while the clinical value of IgM antibodies in antiphospholipid syndrome is not well established.

Objective: The aim of this study was to analyse patients' sera positive for anticardiolipin/B2gp1 antibodies IgM alone and to determine the frequency of monoclonal IgM gammopathy

Method

Methods and patients: In a retrospective study, we selected 25 sera positive for IgM, from a total of 1742 patients routinely tested for anticardiolipin / b2gp1 antibodies over 1 year.

These 25 sera were analysed for gammopathy using Hevylite®**assay (on SPA-Plus Turbidimeter) and confirmed on immunofixation.**

All sera were tested for rheumatoid factor

As control, 25 sera with monoclonal gammopathy were examined for anticardiolipin/ b2gp1 antibodies IgG/IgM using the bioplex system.

Results

Results:

14/25 (56%) sera were positive for IgM (11 IgM λ and 3 IgM κ)

All sera were negative for FR

All control sera were negative for anticardiolipin/ b2gp1 antibodies IgG/IgM

-The positive group for monoclonal IgM included: 5 thrombis, 4 lupus, 2 ITP, 1 WM,

2 CML,

-The negative group included: 3 lupus, 2 thrombosis, 2 ITP, 1 BPC, 1CM**Conclusion**

Conclusion: These preliminary results show the high frequency of IgM gammopathy (over 50%) and suggest a systematic control of its presence. A larger panel of patients is needed to understand its significance.

AUTO1-0673
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

ANTI-PHOSPHOLIPIDE ANTIBODIES IN THROMBOSIS

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Background

BACGROUND: A number of thrombosis are unclassifiable as antiphospholipid syndrome because they don't meet current biological criteria.

The aim of this study was to evaluate a multiplex assay containing conventional (cardio, b2gp1) as well as non-conventional phospholipide antigens and to determine their clinical relevance in thrombotic patients

Method

Patients:

We selected retrospectively sera from 143 patients (pts.) as follows: (93 with thrombotic manifestations and 50 without thrombosis as control).

All sera were previously tested for anti-phospholid, cardiolipine/b2gp1 and Lupus anti-coagulant (LA):

- · Patients with thrombosis:

Group 1: arterial/venous thrombosis (40 pts.)

Group 2: others manifestations (ITP, livedo): (35 pts.)

Group 3: obstetrical manifestations (18 pts.)

- · Control group, without thrombosis:

Group 4: negative for auto-antibodies for systemic disease (20 pts.)

Group 5: with auto-antibodies for systemic disease (30 pts.)

Methodology

Sera were analyzed using "Anti-phospholipide 10 Dot from **Generic Assays**® for detection of following 10 auto-antibodies: anti-cardiolipin, phosphatidic acid, phosphatidyl-choline, -éthanolamine, -glycerol, -inositol, -serine and cofactors anti-B2gp1, annexine5, prothrombin IgG/IgM

Results

		Frequency of positive antibodies	
Specific antibodies	Phospholipids	Thrombosis group	Non thrombosis group
Anti-phospholipid routine test		59%	58%

Anti-cardiolipin	31%	14%
Anti-b2gp1	70%	4%
Anti–annexine	31%	10%
Lupus anti-coagulant(LA)	25%	6%
Anti-prothrombin	48%	10%

Anti-phosphatidyl-choline and –ethanolamine were negative for all patients

The positivity of -anti- phosphatidyl-glycerol, -inositol and –serine, was associated with anti-cofactor antibodies (anti- b2gp1, annexine 5, prothrombin)

Conclusion

This multiplex immunoassay is a quick and easy test to perform. New cofactor targets (annexine-5 and Prothrombin) allow the detection of more APS patients than with currently used assays with higher sensitivity for anti-cardiolipin and b2gp1 antibodies.

AUTO1-0575
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

ARTERIAL VERSUS VENOUS THROMBOSIS IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background

The antiphospholipid syndrome (APS) is a systemic autoimmune disease with few inflammatory manifestations characterized by thrombotic events, pregnancy morbidity and the presence of antiphospholipid antibodies. This syndrome may manifest as a primary disorder, but approximately one third of patients have features of other systemic autoimmune disease (here called secondary APS). The aim of this study was to compare the occurence of arterial and venous thrombosis in patients with APS.

Method

We performed a clinical retrospective study. All patients followed in our department that fulfilled international classification criteria for APS were included. Patients with only pregnancy related morbidity were excluded.

Results

Sixty-five (65) patients aged 48±11 years old were included, 67% were women. In our cohort, a total of 107 thrombotic events were described, being venous thrombosis more frequent (60%). There were 44 patients (67%) with primary APS, whereas the remaining 21 patients (33%) were secondary APS associated mainly with SLE (26%). Patients with primary APS had similar venous thrombosis as patients with secondary APS, but arterial thrombosis appeared to be more frequent in the primary APS group (0,7 events/patient vs. 0,5 events/patient, p=0,10). Patients with primary APS were older (51±10 vs 41±10 years, p=0,001) and had more frequently two or more traditional cardiovascular risk factors (34% of patients vs 19%).

Conclusion

Patients with primary APS had slight increase in arterial thrombosis. These patients were older and accumulated more traditional cardiovascular risk factors, when compared with APS associated with other autoimmune diseases. Therefore, other factors apart from autoantibodies may contribute to arterial thrombosis.

AUTO1-0924
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

BIOLOGICAL TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS. REAL-WORLD DATA FROM THE RUSSIAN NORTH-WESTERN BIOLOGICAL TREATMENT COHORT

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Improvement in the efficiency of complex therapy of rheumatoid arthritis (RA) remains one of the urgent problems of clinical rheumatology. Biologics are drugs that dramatically improved the status of RA patients. At the same time real-world data from large cohorts can give some additional information about efficacy and safety of the biological agents in different populations.
The aim of the study was to analyze the efficacy and safety of biological treatment in large prospective cohort during 102 weeks of treatment.

Methods. The data from 1 400 patients on biological treatment from North-Western State Medical University Biological Treatment Cohort Study (St. Petersburg, Russia) were analyzed. In final analysis data from 758 patients with rheumatoid arthritis, fulfilled EULAR2010 criteria, were included. Biological therapy was performed with the following drugs: adalimumab (n = 22), certolizumab pegol (n = 62), etanercept (n = 64), golimumab (n = 21) and infliximab (n = 69), rituximab (n = 520)). The DAS28 and high-sensitive C-reactive protein (C-RP) were collected as markers of RA activity. Side effects were registered during the study. The approval of the local ethics committee was obtained.

Results. Disease activity, demographic characteristics, and concomitant treatment (including methotrexate, glucocorticoids, NSAIDs, analgesics) in RA patients at baseline were similar in all the treatment groups ($p \geq 0.05$ for all the parameters). The better response was found in golimumab and certolizumab pegol groups at week 6 ($p < 0.01$), fig.1. After week 12 the identical efficacy of all the biological drugs (as first-line therapy) in patients with RA was established (fig.1).

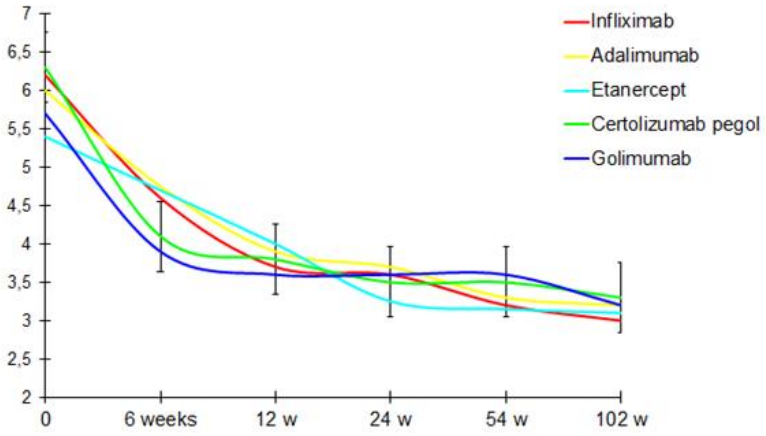

Fig. 1.The dynamics of the disease activity index DAS28 in patients with RA receiving different TNF-a blockers.

C-RP levels were similar in all the treatment groups in all time-points ($p \geq 0.05$). DAS28 (mean ± SD) in RA patients, treated with rituximab, at baseline, and at weeks 24, 54, and 102 was 6.6 ± 2.4, 3.7 ± 1.7, 3.62 ± 2.1 and 3.2 ± 2.05, respectively; $p \geq 0.05$ for the differences with all another treatment groups at the same time-points.
The most frequent side-effects of biological therapy in RA patients were opportunistic infections (bacterial, viral, tuberculosis), OR = 1.8 [95% CI 1.4-2.1]. Risk of infections was higher in patients, receiving monoclonal antibodies to TNFα, as compared to other TNFα inhibitors ($p < 0.01$ for differences between infliximab / adalimumab / golimumab and etanercept, and $p < 0.05$ for differences between infliximab / adalimumab / golimumab and certolizumab pegol).
We have not recorded the increased risk of cancer in RA patients on biological treatment, compared with total Russian population (including lymphomas and skin cancer): for all the tumors OR = 0.98 [95% CI 0.76 - 1.26], for lymphomas OR = 1.23 [95% CI 0.92-1.41], for skin cancer OR = 1.11 [0.88-0.36].

Conclusions. According to the real-world data from the North-Western Biological Treatment Cohort, the efficacy of all the TNFα-inhibitors and rituximab in rheumatoid arthritis treatment after week 12 is the same. Infections, but not tumors, are the most frequent side-effects of biological treatment in rheumatoid arthritis patients.

AUTO1-0265
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

PLATELET ACTIVATION BY ANTIPHOSPHOLIPID ANTIBODIES DEPENDS ON ANTIGEN SPECIFICITY

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Background

Antiphospholipid antibodies (aPL) have been reported to activate platelets. This is considered to be one of the pathogenic properties of aPL. Even though aPL heterogeneity is quite well established, little is known, if the ability to activate platelets is common to all aPL or depends on antigen specificity.

Method

We tested the hypothesis that antiphospholipid antibodies activate platelets in an antigen specificity dependent manner. To further study this issue we analyzed the ability of three human monoclonal aPL with distinctly different antigenic specificities to activate platelets in platelet rich plasma of healthy donors in platelet aggregometry and flow cytometry. The results obtained with human monoclonal aPL were validated with IgG-fractions obtained from patients with APS.

Results

A cofactor independent human monoclonal anticardiolipin aPL had no discernible effect on human platelets. Two monoclonal aPL reactive against b2 glycoprotein I (b2GPI) induced platelet aggregation. These data could be confirmed with patient IgG which could only induce aggregation, if they contained anti-b2GPI activity. To further substantiate platelet activation by anti-b2GPI we analyzed the expression of activation markers on platelets by flow cytometry. Again, only anti-b2GPI antibodies enhanced expression of P-selectin (CD62P) and activated integrin $a_{IIb}b3$ (GPIIbIIIa).

Conclusion

The ability of Antiphospholipid antibodies to activate platelets depends on antigen specificity. Anti-b2GPI aPL activate platelets while cofactor independent anticardiolipin aPL have no effect.

AUTO1-0302
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

SERONEGATIVE ANTIPHOSPHOLIPID SYNDROME OR ANOTHER TROMBOPHILIA ?

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Background

Antiphospholipid syndrome (APS) is the most frequent acquired thrombophilia. The condition has clear classification criteria, last updated in 2006, in Sydney. Sometimes, patients clinically present as APS but do not meet the required criteria (clinical and/or biological ones) in order to be classified as such.

Method

we present the case of a 43 year old male, heavy smoker, moderate drinker, referred to our clinic for calf edema, diffuse abdominal pain and shortness of breath on medium exercise. On clinical examination, the attention in drawn by the intense livedo reticularis, the collateral thoracic and abdominal circulation, and enlarged liver and spleen. A lot of conditions come to mind in face of such a clinical presentation, ranging from Budd-Chiari syndrome to cirrhosis of the liver.
Blood tests revealed inflammation, normochromic normocytic anemia, normal tumor markers, normal values for antiphospholipid antibodies, homocysteine, C protein, S protein, Leyden factor, MTHFR mutation, antinuclear antibodies, on multiple check-ups, more then 12 weeks apart.
Thoracic, abdominal, pelvic CT scan, showed multiple venous thrombi on variate and multiple sites (left internal jugular, complete right internal jugular vein obstruction, massive superior cava vein, etc)

Results

We diagnosed the patient as seronegative APS and started oral anticoagulation with a target INR of 3-4.

Conclusion

Sometimes, one may diagnose a disease, even if the patient does not fulfill the classification criteria of that disease. Furthermore, in this case, even though, seronegative APS might be viewed as an oxymoron, there are times when such a diagnoses is the one that can explain the symptoms of the patient.

AUTO1-0808
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

RIGHT VENTRICLE FUNCTIONALITY IN PRIMARY ANTIPHOSPHOLIPID SYNDROME

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Background

In primary antiphospholipid syndrome (PAPS) the right ventricle (RV) may be affected by pulmonary embolism, cor pulmonale, ischemic cardiopathy, previous left ventricle involvement and obesity. Global longitudinal strain (GLS) measured by speckle tracking echocardiography evaluates myocardial contractility.
Objective: To describe functional alterations of RV in PAPS patients measured by GLS.

Method

Patients with diagnosis of PAPS, >18 years of age with a NYHA class I / II, without severe valvulopathy, and controls matched by age, sex and BMI were included. Transthoracic echocardiogram with measurements of GLS basal, mid and apical segments, systolic pulmonary artery pressure (PAP) and right ventricular ejection fraction (RVEF) was performed. Strain changes consider the absolute value of the number, a more negative value means less contractility of RV. Descriptive statistics/ Mann-Whitney U test were employed.

Results

55 PAPS patients and 45 controls were included, mean age: 48.12+/-12.6 years, disease evolution: 25 +/- 7.6 years. Patients had history of deep venous thrombosis in 73 % and 37% pulmonary embolism. Only 2 patients had history of myocardial infarction. Four patients presented arterial hypertension. GLS was lower in patients than controls: median -19.9 vs. -23, p=0.008, in basal segment -22 vs.-25 (p=0.009) and mid segment -23 vs. -27 (p=0.018). PAP 27 vs. 24 and RVEF: 49 vs. 50, respectively in PAPS and controls (p=NS).

Conclusion

GLS from RV in PAPS patients is altered, as consequence of multiple factors. These alterations may precede the development of pulmonary hypertension. We propose this method as a complementary diagnostic tool.

AUTO1-1019
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

PRE-TRANSPLANT IGA ANTI-B2GPI ANTIBODIES ARE THE MAIN AUTOIMMUNE FACTOR FOR EARLY KIDNEY GRAFT LOSS

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Background

Last decade therapeutic advances in immunesupression, infection control and histocompatibility techniques have increased long term graft survival. However, 5-7% of grafts are still lost at short-term and the underlying mechanisms remain unknown. Aloimmune response is a historically recognized factor for medium and long-term graft loss but aloimmune factors are almost lacking within the first few months post-transplant. Nevertheless, autoantibodies against angiotensin type 1 receptor (AT_1R), endothelin type A receptor (ET_AR) and LG3 fragment of perlecan have been involved recently. In this study we assess whether preexisting autoimmune factors might trigger a response that ends up in early graft loss.

Method

Antibodies against anti-phospholipids, anti-LG3, anti-AT_1R and anti- ET_AR were tested retrospectively at transplant in 361 kidney transplanted recipients from 2008 to 2010 at the Hospital 12 de Octubre (Madrid) and followed up for two years.

Results

At transplant, 7.8% of patients were positive for anti-LG3 antibodies, 10.5% for AT_1R, 1.7% for ET_AR and 30.2% for anti-β2 glycoprotein I (anti-β2GPI). Just patients bearing both IgA anti-β2GPI and IgA:β2GPI circulating immunocomplexes (CIC) had an increased early graft loss within the first six months post-transplant. The vast majority of graft losses occurred within the first month post-transplant and were associated with thrombotic events. None of the remaining antibodies tested were associated with early graft loss.

Conclusion

Preformed IgA anti-β2GPI antibodies at transplant are the main independent autoimmune risk factor for early graft loss within the first six months post-transplant.

AUTO1-1018
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

Antiphospholipid syndrome behind ischemic strokes

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Background

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by a prothrombotic state in presence of persistent antiphospholipid antibodies (aPL). Several manifestations strongly associated with APS are not included as classification criteria, among them some neurological manifestations. The aetiology of several isc hemic strokes is related with the
APS. The aim of the study is to analyze the prevalence of aPL antibodies in the serum samples of patient with recent ischemic stroke.

Method

A total of 136 patients with a recent ischemic stroke were included in the study. Levels of anti-beta-2-glycoprotein I (IgG, IgM and IgA isotypes), IgG/IgM anti-cardiolipin and anti-phosphatidilserin/prothrombin, and IgG anti-annexin A2 antibodies were quantified immediately after the ischemic stroke.

Results

Out of the 136 patients with recent ischemic stroke, 49 (36%) were positive for any aPL antibody. Only 8 (5.9%) were positive for Sidney-consensus aPL. Most of them were positive for non-consensus antibodies (33%). The most prevalent aPL autoantibodies in ischemic stroke patients were the IgA aB2GPI antibodies (21%), following by IgG anti-Annexin A2 (8.1%).

Table 1. Frequency of antiphosholipid antibodies (aPL) in patient inmediatly after an ischemic stroke. (aB2GPI: anti-beta-2-glycootein I, aCL: anti-cardiolipin, aPS/PT: anti-phosphatidilserin-prothrombin, aAn2: anti-Anexin 2).

Antibodies positivity		N=136 (%)
Any aPL		**49 (36.03)**
Consensus aPL		**8 (5.88)**
	aB2GPI o aCL IgG	3 (2.21)
	aB2GPI o aCL IgM	7 (5.15)
No-consensus aPL		**45 (33.09%)**
	aB2GPI IgA	28 (20.59)
	aPS/PT IgG	6 (4.41)
	aPS/PT IgM	8 (5.88)
	aAn2 IgG	11 (8.09)

Conclusion

The evaluation of the aPL included in the classification criteria such as non-consensus antibodies increases the detection capacity of Sroke-patients with APS. This would allow to treat patients at risk of thrombotic event.

AUTO1-1042
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

RECURRENT ARTERIAL THROMBOSIS - A POSSIBLE PARANEOPLASTIC ANTIPHOSPHOLIPID SYNDROME?

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Background

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder consisting in recurrent arterial or venous thrombosis and pregnancy related morbidity in the setting of persistent serum antiphospholipid antibodies (aPL). APS may occur either in the context of an associated disease or as a primary disorder.
It is known that thrombotic events often occur in the setting of malignancy and the association between aPL and malignant tumors as a manifestation of paraneoplastic syndrome has been suggested in various case reports.

Method

We hereby present the case of a 54-year-old female patient with a personal history of breast cancer in 2013 for which she underwent surgery, adjuvant hormone therapy with tamoxifen and radiation therapy. In November 2017 she presented with sudden, severe epigastric pain. Contrast CT scan revealed celiac trunk thrombotic stenosis for which she underwent stenting procedure and was further administered low molecular weight heparin therapy with a positive clinical response. Lupus antiocoagulant was positive with negative results for other autoantibodies. However, given reoccurence of new-onset sharp upper-abdominal pain, a new contrast CT examination was performed, revealing multiple splenic and renal infarctions and the complete obstruction of the previously implanted celiac artery stent.

Results

Continuous heparin infusion was administered with a positive response, followed by oral acenocumarol and double antiplatelet treatment. One month later the patient presented with right brachial and right external iliac artery thrombosis.

Conclusion

Given the multiple arterial thrombotic events occurring in the setting of acenocumarol treatment the patient was started on direct anti Xa factor inhibitor (rivaroxaban) without further events.

AUTO1-0883
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

THE IMMUNE COMPLEXES OF IgG/IgM BOUND TO B-2-GLYCOPROTEIN I ARE ASSOCIATED WITH LIVEDO RETICULARIS, THROMBOCYTOPENIA AND SICCA IN APS PATIENTS

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Background

The aim of this study was to investigate correlation between circulating immune-complexes of IgG or IgM antibodies bound to B2GPI (B2G-CIC and B2M-CIC) and clinical manifestations in Serbian cohort of APS patients.

Method

A total of 57 patients with APS were evaluated: 35 with PAPS and 22 patients with SAPS. Mean age was 47.6±1.6 years; 36 (63.2%) were women. All patients have met the 2006 revised Sydney criteria for APS. Quantification of B2G-CIC and B2M-CIC levels was performed as previously described. For detect B2G-CIC was used anti-human IgG HRP-conjugate and for B2M-CIC human IgM HRP- conjugate, both from INOVA (INOVA Diagnostics Inc., San Diego, CA, USA).

Results

In our cohort Serbian APS patients the prevalence of CIC was 19.29% (11/57); 8 patients with B2M-CIC and the remain 3 patients with B2G-CIC. Livedo reticularis was diagnosed with higher prevalence in patients with CIC compared with patients without CIC; 63.6% and 23.9%, respectively (OR: 5.57, p=0.01). In patients with CIC, thrombocytopenia and leukopenia were more prominent; 54.4% vs 17.4% (OR: 5.70, p=0.01) and 45.5% vs 13.0% (OR: 5.56, p=0.01), respectively. Ophthalmic sicca was more prevalent in patients with CIC; 54.4% vs 8.7% (OR: 12.6, p<0.001). Although complement consumption was more frequent in patients with CIC (Fig.1).

Conclusion

B2G-CIC and B2M-CIC are strongly associated with clinical manifestations related to APS. Widening the APS spectrum is indispensable to better understand this syndrome.B2G-CIC and B2M-CIC are strongly associated with clinical manifestations related to APS. Widening the APS spectrum is indispensable to better understand this syndrome.

AUTO1-1063
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

EXPLORATORY ANALYSIS OF THE PREVALENCE OF HEREDITARY THROMBOPHILIA IN AN ANTIPHOSPHOLIPID SYNDROME COHORT

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Background

The development of thrombosis is multifactorial in Antiphospholipid Syndrome (APS), with other risk factors influencing the thrombotic profile. Previous data suggests that other thrombophilia are rare among APS patients, but some works hint that Protein C and S deficiencies and factor V Leiden mutation are more frequent among APS patients compared to healthy individuals. However, the exact prevalence and clinical implications of the presence of these prothrombotic factors are still poorly characterized.

Method

All patients followed in consultation with a diagnosis of APS fulfilling the Sidney revised criteria were included. Data regarding inherited thrombophilia was collected - Activated protein C resistance (APCR); Leiden V Factor mutation; C and S proteins deficiencies; Prothrombin gene mutation; and Antithrombin III deficiency.

Results

A total of 75 patients were analyzed, with 65.3% corresponding to primary APS. The mean duration of disease was of 6.57 years ± 4.78 years. 17 (22.7%) patients exhibited an inherited thrombophilia: 9 (12%) protein S protein deficiency, 5 (6.7%) APCR, 5 (6.7%) antithrombin III deficiency, 4 (5.3%) C protein deficiency, 2 (2.7%) prothrombin gene mutation and 1 (1.3%) Leiden V factor mutation. The presence of inherited thrombophilia (both individually and unified as a single variable) did not show statistically significant association with particular manifestations of the disease (arterial, venous, specific vessels/territories, or obstetric events) or with recurrence of events.

Conclusion

Although with a significant prevalence in the studied sample, the presence of inherited thrombophilia displayed no categorical clinical significance, a fact that might be related to the sample size originating an underpowered study.

AUTO1-0817
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

AUTOIMMUNE ECOLOGY IN WOMEN WITH RHEUMATIC DISEASES

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INTRODUCTION
The influence of environmental exposure on the risk of developing autoimmune diseases is paramount (i.e., the autoimmune ecology). In fact, environment, more than genetics, shapes immune system.
OBJECTIVE
To evaluate the autoimmune ecology in patients with four autoimmune rheumatic diseases (ARDs).
METHODS
This was an exploratory and self-reported study conducted in 188 women with ARDs namely rheumatoid arthritis (RA, n=51), systemic lupus erythematosus (SLE, n=70), systemic sclerosis (SSc, n=35), and Sjögren's syndrome (SS, n=32). Data were collected by using a structured questionnaire that sought information about demographic and clinical characteristics as well as current or previous exposure to environmental factors associated with autoimmunity. In addition, 14 autoantibodies were measured. Data were analyzed by Spearman correlation and Kruskal-Wallis tests.
RESULTS
General characteristics of patients are shown in Table 1. Previous coffee intake was positively correlated with age at onset of disease in the four ARDs (Figure 1) and it was associated with lower levels of rheumatoid factor (RF) in patients with RA and SSc. Furthermore, heavy metals exposure was associated with higher titers of anti-CCP3 and RF, whereas hair dyes exposure appeared to influence RF and β2glycoprotein-1-IgM (β2GP1-IgM) positivity in RA and SLE respectively (Figure 2).
CONCLUSION
These results confirm the role of environmental exposure in autoimmune phenomena. Coffee intake appeared to influence the age at onset in the four ARDs. In addition, coffee consumption, heavy metals and hair dyes exposure apparently affect the production of CCP3, RF and β2GP1-IgM in patients with RA, SLE and SSc.

AUTO1-0975
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

ANALYTICAL PERFORMANCE OF THE CHEMILUMINESCENT ANALYZER IDS-ISYS FOR THE DETECTION OF ANTI-CARDIOLIPIN AND ANTI-BETA 2 GLYCOPROTEIN I AUTOANTIBODIES

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Background

The objective was to evaluate a new chemiluminescent immunoassay (CLIA, IDS-Isys) using reagents from technogenetics (branded as Zenit RA) for the detection of anticardiolipin (aCL) and anti-beta 2 glycoprotein I (aB2) IgG/IgM autoantibodies (Ab) and to compare them with an in house ELISA used in our reference center.

Method

Samples were related to antiphospholipid syndroms (APS) according to Sapporo criteria n=77, non-APS patients with thrombosis/pregnancy morbidity n=26, non-APS autoimmune diseases (AID) n=23, non-APS/AID disease controls n=30, and healthy controls n=72.

Results

Satisfactory results were obtained for CLIA regarding intra-assay precision (CVs 2.6 to 6.3%, n=30), inter-assay precision (CVs 4.3 to 8.4%, n=30), and inter-sample contaminations. The negative control yielded negative results in all run. At 99th percentile, CLIA demonstrated better sensibility, specificity, PPV, and NPV than ELISA for aCL IgG, aCL IgM and aB2 IgG Abs. Kappa agreement was excellent for aCL IgG Ab (0.759), good for aCL IgM Ab (0.562) and anti-B2 IgM Ab (0.522) and bad for anti-B2 IgG Ab (0.265). A ROC analysis was performed to compare the discrimination power of the assays showing aCL IgG Ab CLIA/ELISA> aB2 IgG Ab CLIA>aCL IgG Ab ELISA>aCL/B2 IgM Ab ELISA>aB2 IgM Ab CLIA. Finally, analyses in principal component and in supervised cluster indicate that CLIA demonstrated the highest ability to predict APS than ELISA.

Conclusion

Autoantibody determination with the chemiluminescent method IDS-Isys is a highly repeatable, reproducible, and accurate method especially in the detection of IgG aCL and IgG anti-B2 Abs which may be considered for laboratory diagnosis.

AUTO1-0269
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

ANTICARDIOLIPIN ANTIPHOSPHOLIPID ANTIBODIES REQUIRE COMPLEMENT ACTIVATION

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Background

APS is an autoimmune disease characterized by thrombosis or recurrent fetal loss associated with persistently elevated titres of aPL. Pathogenic effects of antiphospholipid antibodies (aPL) have been linked to complement activation.

Method

We tested the hypothesis that complement activation by cofactor independent anticardiolipin aPL is needed for their pathogenic role in the APS.

We studied human monocytic cell activation by F(ab)2 fragments of the monoclonal cofactor independent aPL HL5B by analysis of gene induction of TNFα, single stage clotting assay, and confocal microscopy.

Results

In contrast to the intact antibody, F(ab)2 fragments of the anticardiolipin aPL were unable to induce TNFα mRNA or activation of Tissue Factor (TF) on the cell surface of monocytes. The ability to stimulate monocytes was regained by adding a secondary antibody directed against F(ab)2 whereas a secondary antibody against CD4 had no effect. Furthermore, F(ab)2 fragments were not internalized into monocytes unlike intact aPL. Addition of a secondary antibody directed against F(ab)2 restored internalization of the aPL F(ab)2 fragment, while a secondary antibody against CD4 had no effect. And finally, we showed that compstatin had the same effect on HL5B as removal of the Fc-fragment.

Conclusion

Our results demonstrate that the activation of monocytes by cofactor independent anticardiolipin aPL depends on complement activation by the Fc region of the antibody. Without complement activation the internalization of the antibody and all downstream events are prevented.

AUTO1-0837
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

CLINICAL EFFECTIVENESS AND RETENTION RATE OF CERTOLIZUMAB PEGOL IN THE TREATMENT OF RHEUMATOID ARTHRITIS: RETROSPECTIVE ANALYSIS FORM THE MULTICENTRIC ITALIAN REGISTRY LORHEN.

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BACKGROUND AND SCOPE
Certolizumab pegol (CZP) is widely used in clinical practice to treat rheumatoid arthritis (RA). CZP efficacy and safety has been evaluated in RCTs, but real-life data are still lacking. The aim of the study is to analyse the effectiveness and drug persistence of CPZ in a large multicenter cohort of RA patients.

METHODS
We extracted from the Italian LORHEN registry data on all RA patients treated with CZP as first- and second-line biologic drug between December 2010 and April 2017. Drug survival was evaluated by the Kaplan-Meier method and compared according to CZP line of treatment by a stratified log-rank test. EULAR good/moderate response and DAS28 LDA/remission rates were analysed at 12 and 24 months of treatment.

RESULTS
The analysis included 193 RA patients (155 fist-line, 67.9% female, mean age [±SD] 53.9 [±13.5] years, mean disease duration 9.1 [±9.6] years, mean DAS28 4.61 [±1.45], 123/171 positive for rheumatoid factor, 84/118 positive for ACPA, 59% receiving CZP combined with methotrexate). CZP 5-year retention rate was similar in first- and second-line users (43.5% vs 40.5%, respectively; p=0.984). No significant differences were observed in EULAR good/moderate response rates and DAS28 LDA/remission rates between first- and second-line at both 12 (respectively 62.8% vs 54.5%, p=0.82; 55.7% vs 48.5%; p=0.455) and 24 months (respectively 66% vs 60.7%, p=0.65; 56.4% vs 50%; p=0.545).

CONCLUSIONS
In a real-life setting, the 5-year drug survival of CZP was over 40%. Similar response rates were observed in first- and second-line treated RA patients.

AUTO1-0838
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

COMPARATIVE EFFICACY AND RETENTION RATE OF TOCILIZUMAB AND TNF INHIBITORS AS FIRST-LINE BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS: DATA FROM A MULTICENTRE OBSERVATIONAL REGISTRY

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Objectives
To retrospectively evaluate the 6- and 12-month comparative drug survival and remission rate of tocilizumab (TCZ) and TNF inhibitors (TNFis) as first bDMARD in a multicentre observational cohort of Northern Italy (the LORHEN registry).

Methods
All RA patients treated with TCZ or a TNFi as first-line bDMARD from January 2009 to May 2016 and with at least 12-month follow-up were selected from the LORHEN registry. Six- and 12-month clinical remission rate was defined as achievement of disease activity score 28 calculated by using erythrosedimentation rate (DAS28-ESR) <2.6. Drug persistence was calculated by Kaplan-Meier method. The comparison between treatment subgroups was performed by a chi-square test for remission data and by a log-rank test for drug survival. Moreover, DAS28-ESR remission rate has been corrected for drug discontinuation by using the LUNDEX formula.

Results
The overall study population included 884 patients treated with TCZ (n=112) or TNFis (n=772; infliximab 59, adalimumab 238, etanercept 300, golimumab 86, certolizumab pegol 89). Baseline characteristics were similar in the two groups, with the exception of mean age (TCZ 57.1 vs TNFis 53.4 years; p=0.008). Clinical remission was achieved in overall 30.3% patients at 6 months (TCZ 54.4% vs TNFis 26.8%; p<0.001) and in 28.4% patients at 12 months (TCZ 46.6% vs TNFis 25.7%; p<0.001). Similar trends were observed after correction by LUNDEX at 6 (TCZ 45.8% vs TNFis 22.2%) and 12 months (TCZ 35.7% vs TNFis 17.8%).

Conclusions
Despite a similar 1-year retention rate, the proportion of patients achieving DAS28-ESR remission was significantly higher in TCZ treated group compared with TNFis, suggesting a deeper clinical response in patients receiving IL6 blockade.

AUTO1-1028
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

EVALUATION OF A NOVEL MULTI-ANALYTE ASSAY FOR THE DETECTION OF PHOPHATIDYLSERINE/PROTHROMBIN AUTOANTIBODIES AS AN AID IN THE DAIGNOSIS OF ANTIPHOSPHOLIPID SYNDROME (APS)

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Background

Antibodies to phospholids (aPL) and associated proteins are a hallmark in the diagnosis of antiphospholipid syndrome (APS). Recently, the first fully automated bead based system has been developed which allows for the detection of autoantibodies to the phosphatidylserine/prothrombin (PS/PT) complex. This study aimed to analyze the clinical performance of the novel assays in comparison with ELISA using clinically characterized samples.

Method

A total of 140 samples were collected (104 from APS patients and 36 from disease controls) and were tested for anti-PS/PT antibodies (aPS/PT). Antigens were coupled to paramagnetic particles and tested using a novel fully automated particle based multi-analyte system (PMAS) (research use only). All samples were also tested by reference methods for comparison studies. Clinical sensitivity and specificity was calculated for aPS/PT IgG, IgM and IgA isotypes and comparative analysis were performed on the predicate device.

Results

The sensitivity and specificity as well as likelihood and odds ratios for the novel aPS/PT assays were comparable to the ELISA. Interestingly, we for the first time show good discrimination between APS and controls using the IgA isotype (sensitivity 29.8%, specificity 100.0%).

	PMAS PS/PT IgG vs. QL PS/PT ELISA IgG	PMAS PS/PT IgM vs. QL PS/PT ELISA IgM	PMAS PS/PT IgA vs. QL PS/PT ELISA IgA
Total Percent Agreement (95% CI)	80.0% (72.6-95.0%)	79.3% (71.8-85.2%)	89.4% (83.2-93.4%)
Kappa (95% CI)	0.58 (0.45-0.72)	0.57 (0.43-0.70)	0.65 (0.49-0.81)

The correlation between platforms was good for aPS/PT assay for all isotypes.

Conclusion

Our data shows good analytical and clinical performance of the new autoantibody system for the detection of aPS/PT antibodies as an aid in the diagnosis of APS.

AUTO1-0740
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

ANTI-PHOSPHOLIPID ANTIBODIES ARE INDEPENDENTLY ASSOCIATED WITH ATHEROSCLEROSIS IN THE GENERAL POPULATION

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Background

The serum anti-phospholipid antibody (aPLs) prevalence in the general population and the association with cardiovascular (CV) disease is unclear. We aimed to determine the prevalence of aPLs and CV and metabolic comorbidities in a Northern Italian city.

Method

We performed a cross-sectional study on 1,712 adult subjects randomly enrolled in 2010 from the voting lists of Abbiategrasso. All subjects completed a questionnaire for medical history and ongoing/past medications and underwent physical examination and abdomen and carotid ultrasound. Anti-cardiolipin (aCL), anti-beta2 glycoprotein I (aGPI), antiphosphatidylserine-prothrombin (aSP) IgG, IgM, and IgA antibodies were tested in all subjects by ELISA.

Results

APLs were positive in 15.1% of subjects, with no differences between sexes and with highest prevalence rates in older groups. A history of CV events was more frequent in aPLs positive subjects (odds ratio (OR) 1.67, 95%confidence interval (CI) 1.08-2.54, p=0.012), particularly peripheral vasculopathy (crude OR in aPLs positive subjects 2.02; 95CI 1.14-3.57, p=0.015). In subjects with the highest CV risk profile (i.e. with a Framingham risk score >20 and/or diabetes and/or BMI >35), aPLs positivity was associated with the highest risk of CV events (OR 2.52, 95% CI 1.24-5.11, p=0.011). Of interest, aGPI IgA were associated with increased carotid intima-media thickness (adjusted beta 0.51, p= 0.003).

Conclusion

APLs prevalence in our cohort is higher than previously reported, especially in older subjects, but with an equal distribution between sexes. CV events are more frequent in aPLs positive subjects, especially when combined with a high CV risk profile.

AUTO1-0645
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

PREGNANCY OUTCOMES IN A COHORT OF WOMEN WITH ANTIPHOSPHOLIPID SYNDROME. 25- YEARS LONG- TERM OBSERVATION

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Background

The goal of this long-term project was to investigate the course of pregnancy in patients with APS (primary or secondary with SLE) in 1993-2017, to describe the type and severity of it and to explore their relationship with disease-related characteristics. To find specific histological changes in maternal tissue in a subgroup of patients.

Method

During more than 25 years of systematic observation 80 pregnant women with APS were observed and examined. Patients were evaluated every 3 months by a rheumatologist and gynaecologist. Basic demographic data were assessed, In a subgroup of 13 patients a macroscopic and histological examination of maternal tissue was performed in comparison with a healthy control group.

Results

7% missed abortion and 6% of abortions in patients with sec. APS/SLE in second trimester were observed. 75% patients delivered prematurely due to hypertension or preeclampsia, 10% due to growth retardation of fetus. AV heart block of 3rd degree was observed in 1 newborn No congenital malformations were observed in our group. Higher score of maternal infarcts and decidual pathological changes with deposits of immunocomplexes were found in microscopic examination in patients with APS in comparison with healthy controles. Signs of accelerate aging, nodules and inflammatory infiltration and higher score of deposits of immunecomplexes were found.

Conclusion

The results of our long terms study showed a good outcome of pregnancy. Higher rate of complications was found in the group with sec. APS with SLE.

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AUTO1-0256
ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE

PERSISTENT POLYCLONAL B LYMPHOCYTOSIS WITH PRESENCE OF ANTIPHOSPHOLIPID ANTIBODIES. 2 CASE STUDIES.

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Background

Persistent polyclonal B-lymphocytosis (PPBL) is a rare benign hematological disorder described in 1984. It is chronic lymphocytosis (>4x10^9/l), which occurs in most cases in adult women, often in smokers. Increased B-lymphocytes have the character of mature B-lymphocytes. IgM-hypergammaglobulinaemia and the positivity of HLA-DR7 are often observed. The authors report two cases of women with PPBL and a significant presence of antiphospholipid antibodies (APLA) and a clinical picture of the spectrum of antiphospholipid syndrome.

Method

Case reports.

Results

i. Female born in 1964. Since 10/1994 bronchial asthma - severe form requiring administration of systemic corticosteriods. Smoking until the 90s, 3 births, 2 spontaneous abortions. PPBL together with significant IgM-hypergammaglobulinemia since the beginning of monitoring. Further increase of APLA, IgG-hypogammaglobulinemia, mild splenomegaly, chronic cephalea, MRI of the brain with diffuse multiple gliotic changes on both hemispheres, variable thrombocytopenia.

ii. Female born in 1970. Since 2000 she has been monitored for antiphospholipid syndrome after two abortions. Permanent smoker. In treatment with LMWH the birth of healthy twins in 3/2001. In 7/2007 psedotumor of the right orbit with a good response to corticotherapy. In 11/2008 PPBL was detected, stable in the long-term follow-up. But in following years increasing trend of IgM has been found simultaneously with decreasing of IgG and increasing of APLA.**Conclusion**

The authors present the detailed immunological characteristics of two cases and discuss a possible connection to PPBL. Due to prognostic uncertainty of PPBL towards the formation of malignant lymphoproliferative disease, long-term follow-up of such cases is required.

AUTO1-0455
CANCER AND AUTOIMMUNITY

LACK OF CORRELATION BETWEEN EFFICACY AND AUTOIMMUNITY IN 47 MELANOMA PATIENTS TREATED WITH IPILIMUMAB

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Background

Ipilimumab was the first immunotherapy approved for metastatic melanoma in decades and is currently registered as a second-line treatment. However, new immunotherapies, in combination with ipilimumab, offer even better clinical outcomes for patients compared with single-agent treatments, at the expense of improved toxicity.The aim of this study was to evaluate the feasibility of ipilimumab outside the clinical trials and to identify survival predictors for treatment benefit.

Method

Data were collected on 47 advanced melanoma patients treated with ipilimumab between 2010 and 2015 at a single center. Association of clinical characteristics (including primary tumor characteristics), serum lactate dehydrogenase (LDH), erythrocyte sedimentation rate, absolute eosinophil, lymphocyte, and neutrophil count, neutrophil/lymphocyte and eosinophil/lymphocyte ratio with toxicity and clinical outcome were assessed using univariate and multivariate analysis

Results

Median progression-free survival at a median follow-up of 10 months was 2.7 months and median overall survival wa**s** 9.8 months. Objective response was observed in 17% of patients and the disease control rate at week 24 was 40%. The 1- and 2-year survival rates documented were 40% and 28%, respectively. Significant association between high LDH level (>1.5× upper limit of normal) and decreased overall survival was demonstrated in uni- and multivariate analysis (hazard ratio [HR]: 3.554, 95% CI: 1.225–10.306, p=0.019). Neither biomarkers nor clinical outcome were associated with toxicity.

Conclusion

Using baseline serum LDH to identify patients most likely to benefit from ipilimumab therapy could serve as a simple and inexpensive biomarker of clinical outcome. No correlation was observed between immune-related side effects and clinical outcome.

AUTO1-0271
CANCER AND AUTOIMMUNITY

DUCTAL ADENOCARCINOMA RELATED GRANULOMATOSIS WITH POLYANGIITIS IN THE BREAST

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Background

We report a rare case of systemic Granulomatosis with polyangiitis that was presented as an ulcerative breast tumor following quadrantectomy due to ductal adenocarcinoma. The patient was a 61-year-old woman who had previously developed high grade ductal carcinoma in the right breast. Quadrantectomy was performed. During the postoperative radio and hormontherapy the patient developed proteinuria and renal insufficiency. Renal biopsy and highly elevated anti-PR-3 ANCA level provided the diagnosis of GPA. The combination of methylprednisolone and azathioprin therapy was applied for remission induction, commencing a maintenance regimen with azathioprin monotherapy resulting in remission.

Method

Three years later she re-presented a therapy-resistent ulcerative tumor in the right breast. Skin biopsy provided the histological evidence of GPA without the presence of tumor cells. The level of anti-PR-3 ANCA was again highly elevated, however during the relapse we have found no renal involvement. The patient received azathioprin combined with high dose methylprednisolone which was tapered down gradually. Although wound healing was initiated due to the combined parenteral and local treatment, we performed total mastectomy to eliminate the paraneoplastic origin of the GPA.

Results

After methyprednisolone was tapered down gradually, the patient is on azathioprin maintenance therapy showing no signs of relapse. Her serum anti-PR-3 ANCA titer is within the normal range.

Conclusion

In case of ductal adenocarcinoma partial removal of the breast might be ineffective. Rarely, GPA can be paraneoplastic. In the literature 28 similar case was reported during 30 years.

AUTO1-0722
CANCER AND AUTOIMMUNITY

THE ROLE OF NON-CODING RNA IN IMMUNE REGULATION THROUGH NLRP3 INFLAMMASOME

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Background

It has been reported that dysregulation of long non-coding RNAs (lncRNAs) in immune cells might contribute to the pathogenesis of autoimmune diseases. Non-coding transcript in T cells (NTT) is a nuclear lncRNA first discovered in activated T cells. The regulations of immune response are complex, and the known factors in immune regulation include lncRNAs, inflammasome and extracellular pH.

Method

We detected the expression levels of NLPR3, NTT and several immune-related genes which locate near NTT gene in acidic pH treated cancer cells and rheumatoid arthritis (RA) patient cells. And DNA Chromatin Immunoprecipitation (ChIP) assays were used to investigate NTT and NLRP3 interactions. We also used next generation sequencing (NGS) to explore the genome wide effect of acidic pH treatment.

Results

We found the downregulation of NTT and upregulation of NLPR3 in acidic pH treated cancer cells. We also discovered that NLRP3 binds on NTT promoter and knockdown of NLRP3 cause NTT upregulation, indicating the inhibitory effect of NLRP3 on NTT expression. And the expressions of several immune-related genes which locate near NTT gene, such as TNFAIP3 and IFNGR1, increased in acidic pH treatment. In addition, our result showed that the expression of NTT was upregulated in peripheral blood mononuclear cells (PBMCs) of rheumatoid arthritis (RA) patients.

Conclusion

Our results show that lncRNA NTT expressions were regulated by extracellular pH through NLRP3 inflammasome interaction. And the expression of NTT significantly increased in PBMCs of RA patients, which might contribute to abnormal immune regulation. Therefore, the role of NTT in autoimmunity needs further investigation.

AUTO1-0692
CANCER AND AUTOIMMUNITY

TWO-YEARS FOLLOW UP EVOLUTION IN A CASE OF TRASTUZUMAB -INDUCED PULMONARY SARCOIDOSIS

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Background

Trastuzumab ,a monoclonal antibody against HER2 , is a targeted therapy for HER2 Positive Breast Cancer .Only three case reports in literature described Trastuzumab induced diffuse sarcoid-like pulmonary disease ,none of them follow up patients for a longer period.

Method

Case Report

Results

We report the case of a 50-year-old woman diagnosed with ductal carcinoma of the right breast (2012) stage p (2)T1pN0M0, tumor ER positive ,PR negative and HER 2 positive. Successfully completed chemotherapy (EC), radiotherapy and started Trastuzumab therapy 530mg/every three weeks well tolerated for 12 applications. At the end of treatment , patient presented respiratory symptoms :cough and dyspnea, CT scan revealed mediastinal adenopathy , reconfirmed at PET-CT . To exclude metastasis ,lymph node biopsy was performed by mediastinoscopy .Histopathology examination revealed non-necrotizing granulomas suspicious for sarcoidosis, confirmed in IHC. Normal ACE levels but high levels for sIL-2R . Patient started systemic corticotherapy with oral Metilprednisolon initial dose 1mg/kg/day then slowly tapered ,stopped after one year. Good evolution in clinical and imagistic terms with resolution of mediastinal adenopathy , results maintained even after two years.
Discussion: This rare reaction of Trastuzumab treatment is important to be differentiated for neoplastic disease progression. Is still a matter of debate if is a truly adverse reaction or is a part of it's complicated mechanism of action ,not yet completely understood.

Conclusion

This case report with good evolution at two-years follow-up may support that sarcoid-like reaction during Trastuzumab treatment is a part of healing process due to it's mechanism of action.

AUTO1-0760
CANCER AND AUTOIMMUNITY

PARANEOPLASTIC NEUROLOGICAL AUTOIMMUNITY ASSOCIATED WITH ANNA-1 AUTOANTIBODY

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Background

The ANNA-1 or anti-Hu antibodies are directed against an antigen localized in the nucleus of all neurons. They are directed against a family of RNA binding proteins with a molecular size of 35-40 kDa. They are expressed in the nuclei of neurons of the central and peripheral nervous system. Paraneoplastic syndromes associated with this antibody are sensory neuropathy, encephalomyelitis, cerebellar degeneration with autonomic dysfunction and limbic encephalitis. The tumours associated with the presence of this antibody are small cell lung cancer, prostate cancer, breast cancer, neuroblastoma and sarcoma.

Method

We report five patients with paraneoplastic syndromes and the presence of anti-Hu antibodies were detected. Onconeural antibodies were identified in serum sample by indirect immunofluorescence (Euroimmun) and the positive results were confirmed on immunoblot assay (Euroimmun).

Results

The results obtained are shown in the table.

Gender	Age (years)	Paraneoplastic syndromes	Antibody	Diagnosis of the patient after study	Survival
Male	79	Limbic encephalitis	Anti-Hu 1/100	Squamous cell lung cancer	Deceased (2 months)
Male	67	Paraneoplastic encephalitis	Anti-Hu 1/1000	Lung adenocarcinoma	Deceased (19 months)
Female	50	Paraneoplastic encephalitis	Anti-Hu 1/1000	Small cell lung cancer	Deceased (7 months)
Female	76	Paraneoplastic encephalitis	Anti-Hu 1/100 + anti SOX 1/100	Squamous cell carcinoma of the tonsil	Deceased (9 months)
Female	52	Sensory neuropathy	Anti-Hu 1/100	Hidden Tumour	Alive

Conclusion

The presence of anti-Hu antibodies was associated to cancer in four patients while in the remaining patient was not found a tumour. In these four patient, the presence of anti-Hu antibodies was associated with a poor prognosis with short survival time. In summary, the presence of this antibody should help the clinician towards finding a hidden tumour, foremost among them, small cell lung cancer presents in 80% of cases of positivity for this antibody.

AUTO1-0870
CANCER AND AUTOIMMUNITY

CLINICAL CHARACTERISTICS INDICATIVE OF PARANEOPLASIA IN ADULT DERMATOMYOSITIS PATIENTS

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Background

While some clinical features are reported as risk factors for cancer-associated dermatomyositis (DM), most results are conflicting with paucity in the literature regarding paraneoplastic DM. The aim of this study was to determine clinical symptoms, which are indicative specifically for a paraneoplastic etiology.

Method

A retrospective analysis of adult patients who were diagnosed with dermatomyositis between January 1998 and January 2014 was performed. Demographic data, the presence or absence of objective and subjective symptoms, initial and follow-up treatments, and the times of relapses were examined.

Results

In all, 30 idiopathic and 11 paraneoplastic DM cases were reviewed and compared. Of the cutaneous symptoms, heliotrope rash with a profound periorbital oedema (43.3% vs 81.8%%; p=0.038), pruritus (16.7% vs 63.6%; p=0.007) and skin ulceration (0.0% vs 27.3%; p=0.015) were found to be associated with a paraneoplastic etiology. In addition, respiratory muscle involvement (3.3% vs 36.4%; p=0.014), lower creatine kinase increase (3355.9 ± 53116 vs 1009 ± 813.3; p=0.037), lack of ANAs or ENAs (40.0% vs 100%; p=0.002) and absence of immunecomplex deposits in the intramuscular vasculature of the skeletal muscles (16.7% vs 72.7%; p=0.001) also showed a positive association with paraneoplasia.

Conclusion

The clinical manifestations of paraneoplastic DM differ from previously described cancer-associated DM risk factors. This indicates a need for etiological stratification when assessing malignancy-associable features in future studies.

AUTO1-0180
CANCER AND AUTOIMMUNITY

SOX-1 AUTOANTIBODIES IN PARANEOPLASTIC SUBACUTE CEREBALLAR SYNDROME: A CASE REPORT

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[2]Division of Medical Oncology- Catholic University of Sacred Hearth- Rome- Italy, Medical Oncology, Rome, Italy

Background

Paraneoplastic neurological syndromes (PNS) are tumor-associated disorders witch are not caused by the tumor or metastasis. Different antibodies have been associated with these syndromes this suggested another pathogenesis.

Anti SOX-1 antibodies are associated with different PNS, and have been described in Lambert-Eaton myasthenic syndrome and in paraneoplastic cerebellar degeneration.

Method

We report the case of a 50 years old woman who presented, since 2 month, lower extremity muscle fatigue, dysarthria, staggering gait, nystagmus, dizziness, diplopia and bilateral dysmetria; the clinical feature suggested subacute cerebellar syndrome.

Brain MR did not show any significant change.

Lung CT showed left parahilar tumor, infiltrating superior vein and pulmonary artery and the left bronchus. A small-cell lung carcinoma was diagnosed by lung biopsy.

We immediately started intravenus Immunoglobulin (160mg) and hight dose of dexamethasone therapy that improved the clinical sintoms. The patient started chemiotherapy with Carboplatin (AUC4) and Etoposide (100mg/m^2).

We tested antineural antibodies pre therapy (anti-Hu, anti-Ri, anti-Yo, anti-amphipysin, anti-Sox-1, anti-Ma1, anti-Ma2, anti-Tr, anti-Zic4, anti-GAD65).

Results

Screening immunoflorescence (IIF; Neurology Mosaic1 Euroimmun) test for the detection of antibodies against neuronal antigens showed a granular fluorescence in primate cerebellum and grey matter nuclei. Line blot test (Alifax) confirmed the IIF and identified the antigen responsible as SOX-1.

IIF and immunoblot post therapy were negative.

Conclusion

In conclusions we suggest to test neuronal autoantibodies in case of neurological syndromes with unknown pathogenesis and negative brain imaging that may disclose a tumoral lesion. We confirm the correlation between SOX-1 autoantibodies and small cell lung carcinoma that have been already described in few literature reports.

AUTO1-0661
CANCER AND AUTOIMMUNITY

ATYPICAL MITOTIC IFL PATTERNS ON HEP-2 CELLS AND CANCER ASSOCIATION

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Background

An association between given autoimmune diseases and some cancers is well established. With the advent of immune-checkpoint immunotherapy for cancer many patients are tested for autoantibodies prior to treatment and this constitutes an opportunity to investigate systematically tumor-associated autoantibodies.

Method

We selected cases reported as "atypical mitotic pattern" on ANA tests among all the samples tested from 2015 to 2017. ANA were detected by IFL on HEp-2 cells (INOVA Lite®, INOVA Diagnostics, Werfen). Positive sera were classified according the International Consensus on ANA patterns; we included a group with a "Pleomorphic-not-PCNA" pattern. Clinical records were reviewed for cancer diagnosis and tumor markers.

Results

From 36.541 ANA tests, 44 from 22 patients were reported as "atypical mitotic pattern": 13 Pleomorphic-not-PCNA, 6 CENP-F-like and 3 mitotic chromosomal coat. Clinical records revealed that 5/22 had a cancer diagnosis (4 CENP-F-like and 1 Pleomorphic-not-PCNA-Nop-52-like). Tumor markers were available in 8/22 patients and found positive in 5, of whom 2 showed a mitotic chromosomal coat pattern without a malignancy at the time of the study.

We have confirmed that the CENP-F-like pattern is strongly associated to malignancy (67% of the cases). Interestingly, 2 out of the 3 patients positive for the mitotic chromosomal coat pattern had positive tumor markers.

Conclusion

Even if systematic studies in stratified series are required to confirm these preliminary data**,** these results suggest that the detection of atypical patterns in ANA screening could be useful to alert on the possibility of a malignancy.

AUTO1-0379
CANCER AND AUTOIMMUNITY

NK-CELL-MEDIATED NEUROBLASTOMA CELL LYSIS IS ENHANCED BY IgG FROM PATIENTS WITH PAEDIATRIC OPSOCLONUS-MYOCLONUS-SYNDROME (OMS)

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Background

Paediatric opsoclonus-myoclonus-syndrome (OMS) is a rare autoimmune disorder and about 50% of OMS are associated with a neuroblastoma. Since surface-binding autoantibodies directed against neuroblastoma and cerebellar neurons have been demonstrated, an autoimmune aetiology is suspected. Interestingly, patients with OMS may have a better prognosis of the tumor disease. We investigated, whether surface-binding autoantibodies in OMS can induce antibody-dependent cell-mediated cytotoxicity by NK-cells.

Method

The neuroblastoma cell-line Kelly was incubated with OMS IgG or IgG from patients with neuroblastoma without OMS or healthy controls and co-cultured with Natural Killer (NK) cells (NK-92 cell line). The cytotoxic effects were measured by LDH release.

Results

IgG from patients with OMS induced a higher NK-cell-mediated cytotoxicity than IgG from patients with neuroblastoma or healthy controls ($p<0.05$). Upregulation of MHC class I in neuroblastoma cells reduced the NK-cell-mediated cytotoxicity.

Conclusion

Activation of NK-cells might be an additional mechanism of an anti-tumour immunity in children with paediatric paraneoplastic opsoclonus-myoclonus-syndrome and may contribute to the favourable prognosis of OMS children.

AUTO1-0071
CANCER AND AUTOIMMUNITY

THE ROLES AND APPLICATIONS OF AUTOANTIBODIES IN HUMAN MALIGNANT TUMOURS

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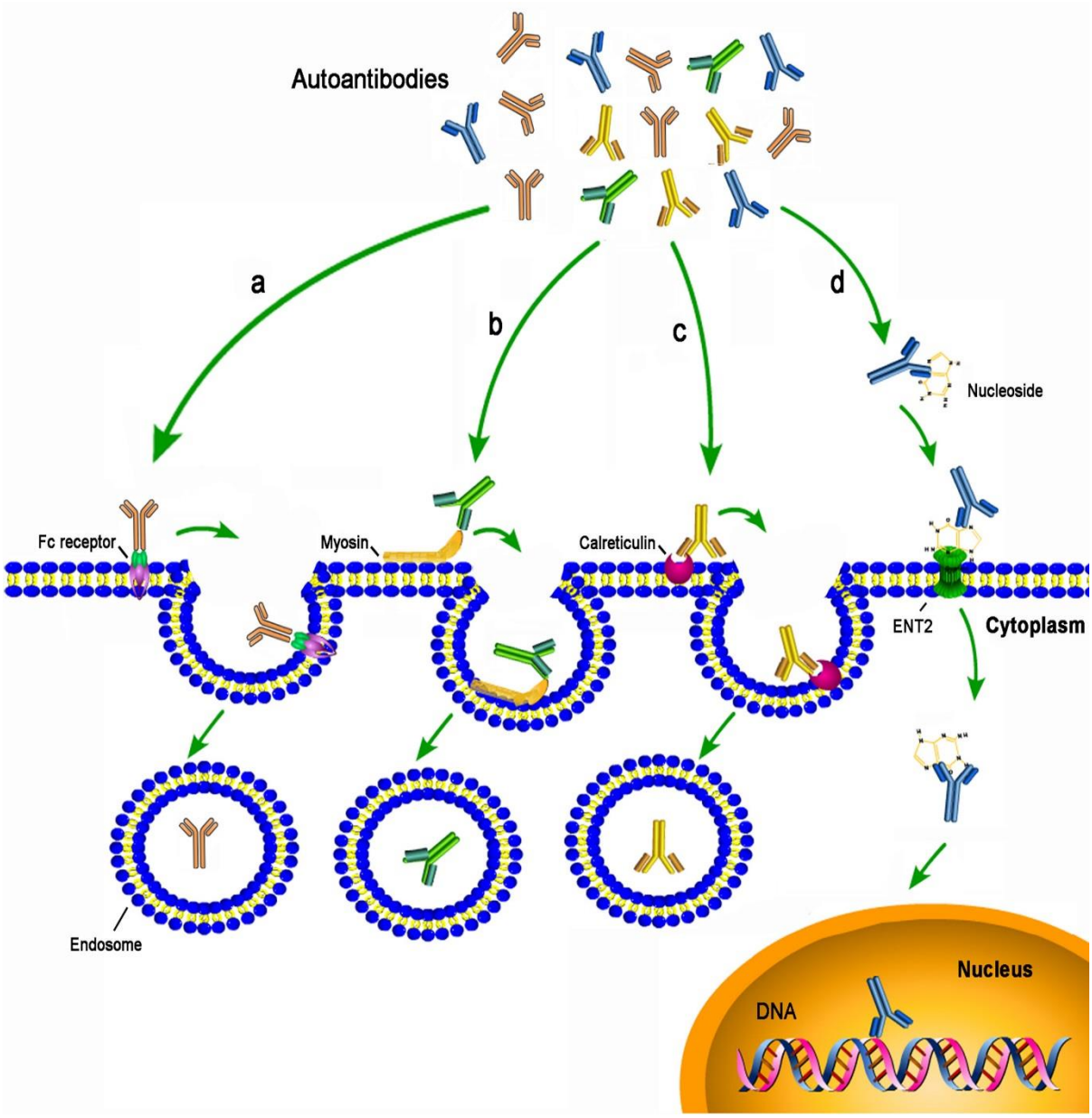
Background

Over the past few decades, numerous epidemiological studies have shown that the risk of certain cancers is significantly altered in patients with autoimmune diseases, which suggests that autoantibodies may play either promoting or suppressing roles in cancer progression. Because the cancer cells generate neoantigens, which trigger the immune system to produce autoantibodies, serum autoantibodies against tumour-associated antigens (TAAs) have been established as a novel type of cancer biomarkers and have been extensively studied in different types of cancer.


Autoantibodies
a
b
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Nucleoside
Fc receptor
Myosin
Calreticulin
ENT2
Cytoplasm
Endosome
Nucleus
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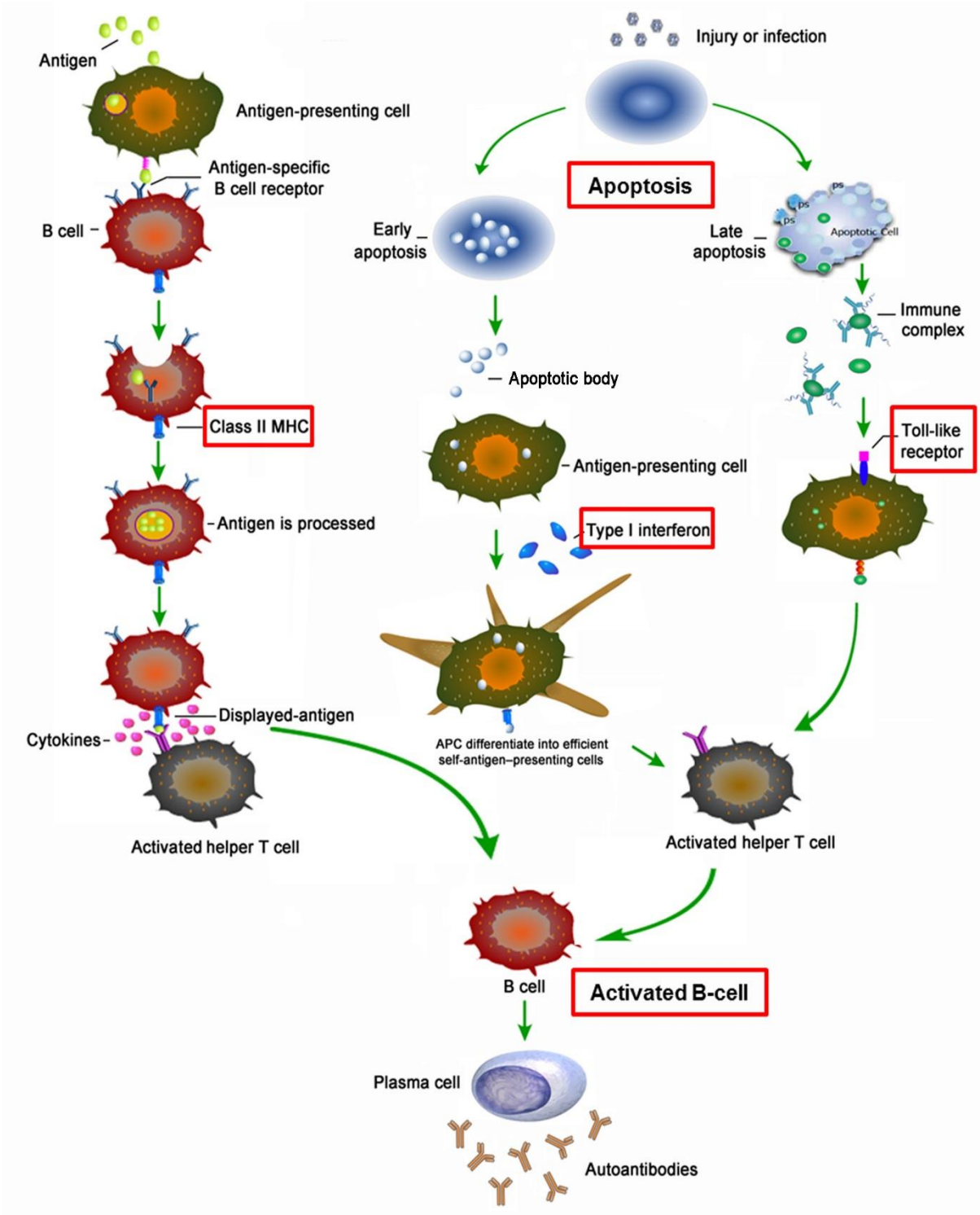
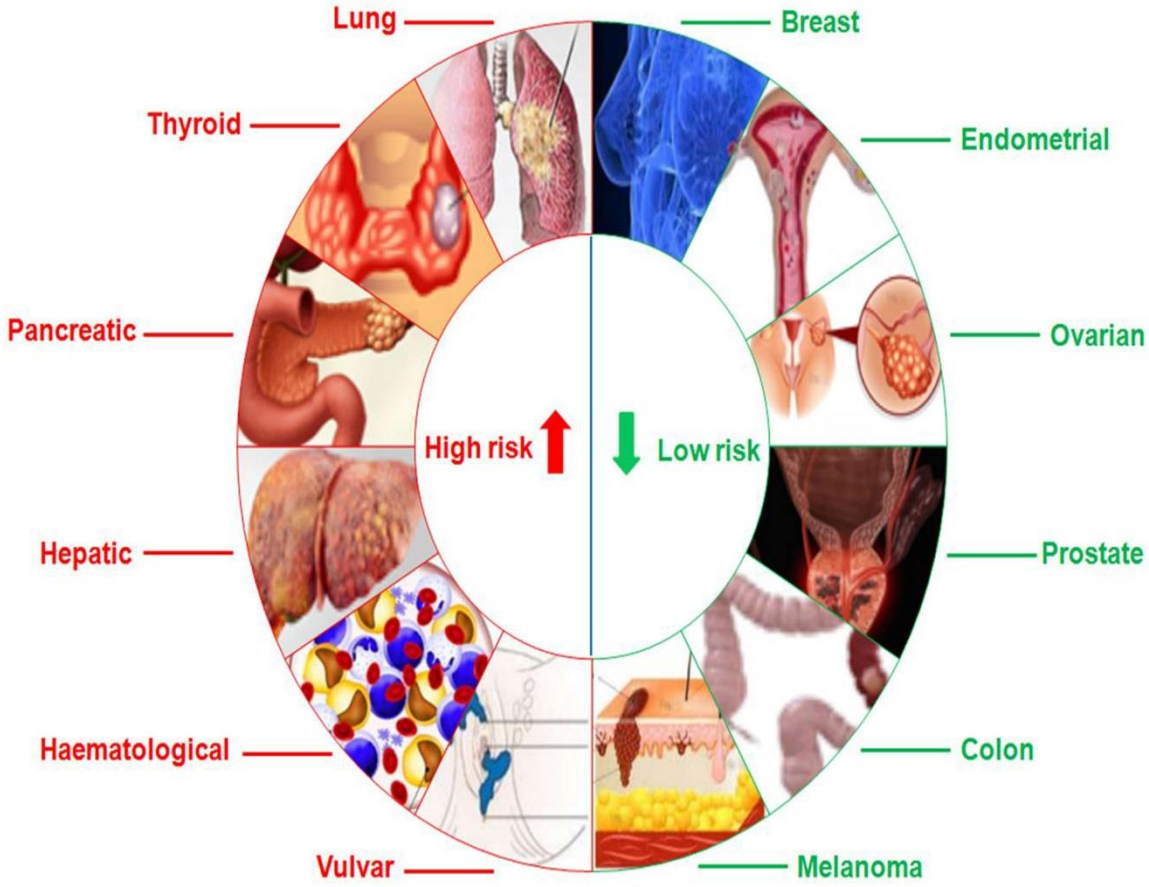


Method

The autoantibodies as biomarkers in cancer diagnosis are not only more sensitive and specific than TAAs, but also could appear before clinical evidences of the tumours, thus disclosing them. The observations that cancer risk is lower in patients with some autoimmune diseases suggest that certain autoantibodies may be protective from certain cancers. Moreover, the presence of autoantibodies in healthy individuals implies that it could be safe to employ autoantibodies to treat cancer. Of note, autoantibodies derived from lupus murine model received much attention due to their selective cytotoxicity for malignant tumour cell without harming normal ones.

Results

We also found a lupus-derived monoclonal autoantibody could inhibit tumour proliferation. These studies showed the therapeutic value of autoantibodies in cancer. In this review, we revisited the pathological or protective role of autoantibodies in cancer progression, summarize the application of autoantibodies in cancer diagnosis and prognosis, and



Conclusion

Autoantibodies could not only regulate cancer progression but also promise to be valuable instruments in oncological diagnosis and therapy.

AUTO1-0479
CELIAC DISEASE AND AUTOIMMUNITY

EVALUATION OF ANTI-ENDOMYSIAL ANTIBODIES ON NOVA VIEW® AUTOMATED FLUORESCENCE MICROSCOPE

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Background

Automation of indirect immunofluorescent (IIF) assays has the potential to improve reproducibility and eliminate subjectivity of testing while simultaneously improving workflow and efficiency. The purpose of this study was to compare the performance of NOVA View®, a computer-aided automated fluorescence microscope, to that of the traditional manual method for the detection of anti-endomysial antibodies (EMA) using a clinically characterized cohort of samples from patients with Celiac Disease (CD).

Method

The study included 538 samples from patients with CD (n=173) and relevant disease controls (n=365). All samples were tested on NOVA Lite® DAPI EMA Kit (Inova Diagnostics, USA) and run on NOVA View, during which DAPI stained nuclei were used to detect the location of the muscularis mucosa. An image was produced for interpretation by a trained technologist. The same slides were subsequently read with a manual fluorescence microscope by the same technologist.

Results

In the clinical cohort population, NOVA View digital image reading and manual reading showed similar clinical performance (see table). In addition, NOVA View digital image reading and manual reading showed a high level of agreement (overall agreement =

99.4%, Cohen's *kappa* = 0.98).

Subjects / Diagnosis	Positive/Total	% Positive	Positive/Total	% Positive
Celiac Disease (CD)				
On gluten	78/90	87%	78/90	87%
On gluten-free diet	30/83	36%	30/83	36%
Dermatitis Herpetiformis (DH)	7/18	39%	6/18	33%
Normal Blood Donors	0/109	0%	0/109	0
Disease Controls (gastro intestinal)				
Crohn's Disease (CrD)	0/49	0	0/49	0
Ulcerative Colitis (UC)	0/20	0	0/20	0
Autoimmune Gastritis (AIG)	0/15	0	0/15	0
Disease Controls (other)				
Autoimmune Hepatitis (AIH)	0/19	0	0/19	0
Epstein-Barr Virus (EBV)	0/5	0	0/5	0
Human Immunodeficiency Virus (HIV)	0/20	0	0/20	0
Primary Sclerosing Cholangitis (PSC)	0/10	0	0/10	0
Systemic Lupus Erythematosus (SLE)	1/20	5%	1/20	5%
Systemic Sclerosis (SSc)	0/20	0	0/20	0
Syphilis (SYPH)	0/15	0	0/15	0
Autoimmune Thyroiditis (AT)	0/25	0	0/25	0
Rheumatoid Arthritis (RA)	0/20	0	0/20	0

Conclusion

This study demonstrates that the new EMA module on the NOVA View automated system generates digital images that are equivalent to manual microscopy. NOVA View is an attractive option for labs who want to automate and streamline the reading and interpretation of the traditional fluorescent microscopy.

AUTO1-0505
CELIAC DISEASE AND AUTOIMMUNITY

CHARACTERIZATION OF CELIAC DISEASE AMONG ADULTS

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Background

Celiac disease (CD) is an immune-mediated enteropathy, diagnosed at any age, with a peak at early childhood and at the fourth and fifth decade of life for women and men, respectively. It is considered that 50% of the patients present with atypical symptoms. Our main goal is to address the prevalence and clinical features of CD in adults.

Method

Anti-endomysium (EMA), anti-tissue transglutaminase (TTG) and anti-gliadin peptides autoantibodies were evaluated in 3267 adults with clinical suspicion of CD, between January 2010 and July 2017. Anti-EMA was detected by indirect immunofluorescence, anti-TTG and anti-gliadin were measured by fluorescent enzyme immunoassay (Euroimmun®).

Results

Anti-EMA and anti-TTG were positive in 39 patients (1.2%): 31 women and 8 men. The mean age among women, was 35.8±13.9 and among men was 43.5±20.0. Four patients were aged between 70 and 82 years. 5 patients had type 1 diabetes, 6 patients had other autoimmune diseases and 2 patients presented dermatitis herpetiformis. Regarding clinical presentation: 61.5% of the patients referred diarrhea/constipation, abdominal pain and pruritic eruption; 25.6% were diagnosed with therapy-refractory anemia and 12.8% of the patients had bowel complaints and anemia. 33.3% of the patients that performed duodenal biopsy were grade 3 in the Marsh modified classification.

Epidemiological, clinical and histological characteristics of the adult patients with celiac disease		
	Women	Men
Number	31(79.5%)	8(20.5%)
Age	35.8±13.9 (min: 19 years; max: 75 years)	43.5±20.0 (min: 18 years; max:82 years)
Clinical presentation		
24 patients (61.5%) presented diarrhea/constipation, abdominal pain and pruritic eruption, osteopenia, without anemia or biochemical alterations	10 patients (25.6%) presented therapy-refractory anemia without other clinical manifestations: ▪macrocytic anemia: 2 patients (5.1%) ▪normocytic normochromic: 2 patients (5.1%) ▪microcytic hypochromic anemia: 6 patients (15.3%)	5 patients (12.8%) presented diarrhea/constipation, abdominal pain and microcytic hypochromic, osteopenia, anemia or biochemical alterations
Other pathologies identified in celiac patients		
▪6 patients (15%) had autoimmune diseases (inflammatory bowel disease, autoimmune hepatitis, systemic lupus erythematosus and Raynaud syndrome), ▪5 patients (12.8%) were type 1 diabetes, ▪2 patients (5.1%) presented dermatitis herpetiformis		
Classification of histologic findings in duodenal biopsies according the Marsh modified classification		
15 patients (38.5%) did not perform the biopsy	24 patients (61.5%) performed duodenal biopsy. •2 patients presented a grade 2 •7 patients presented a grade 3a •2 patients presented a grade 3b •4 patients presented a grade 3c •1 patient did not presented alterations. 8 patients performed the biopsy after the beginning of the gluten-free diet.	

Conclusion

The prevalence of CD among our patient population is according to the prevalence in Europe. Most of the patients presented atypical symptoms, which may contribute to the delay in the diagnosis, for the severity of histological changes and to the underestimation of the prevalence of CD.

AUTO1-0958
CELIAC DISEASE AND AUTOIMMUNITY

EUROARRAY HLA-DQ2/DQ8-H DIRECT AND OLERUP SSP FOR THE DETERMINATION OF CELIAC DISEASE ASSOCIATED RISK FACTORS HLA-DQ2.2, -DQ2.5 AND -DQ8 – A COMPARATIVE STUDY

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Background

The heterodimeric human leukocyte antigens (HLA) DQ2 (HLA-DQ2.2 and HLA-DQ2.5) and DQ8 are strongly associated with celiac disease (CD). The α- and β-subunit of HLA-DQ2 and -DQ8 are encoded by certain alleles of the HLA genes DQA1 and DQB1 (figure 1). Homozygous carriers for DQ2.2 and DQ2.5 have a higher risk of disease development compared to heterozygous individuals. In this study the concordance rate between the new EUROArray HLA-DQ2/DQ8-h Direct and the Olerup SSP® tests in the detection of CD relevant HLA-DQ alleles and gene dose is evaluated.

Method

81 serum samples of suspected CD patients were included in this study. In the EUROArray test amplification of selected HLA-DQ gene sequences is achieved by two parallel multiplex PCRs with simultaneous fluorescence labelling of the reaction products for subsequent hybridization. All relevant HLA-DQ genotypes are automatically deduced by the EUROArrayScan software. In the Olerup test system determination of HLA-DQ alleles is achieved by 72 parallel singleplex PCRs with subsequent gel electrophoresis and semi-automated result output

Results

The study showed 100% concordance between the two test systems regarding the determination of homozygous and heterozygous DQ2.2, DQ2.5 and DQ8 genotypes (table 1).

Conclusion

The concordance rate of 100% confirms highest reliability of both tests for determination of CD risk, including discrimination of CD relevant homozygous and heterozygous states. The EUROArray test is easier to perform since evaluation is fully automated and lab work reduced to 2 multiplex PCRs and a single array incubation compared to 72 parallel PCRs required for Olerup tests.

AUTO1-0333
CELIAC DISEASE AND AUTOIMMUNITY

SERONEGATIVE CELIAC DISEASE IN ADULTS

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[2]*Universitary Hospital Niño Jesus, Clinical Laboratory, Madrid, Spain*

Background

Coeliac disease(CD) is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed people.

CD serology detection in adult population, was much less efficient than in pediatric population. The prevalence of seronegative CD in adults is 6–22% of all diagnosed cases.

Patient:

A 52 year old, for two years referred diarrhea abdominal pain, steatorrheic depositions, myalgias, asthenia, history of Graves disease and sarcoidosis.

Method

Serological markers(SM). Anti-transglutaminase antibodies, anti-endomysial antibodies, biochemical and hematological profiles. HLA typing DQ2 and DQ8.

Results

SM were negative, the patient ruled out an intestinal biopsy, a genetic study was requested.

The result of the genetic study: HLA-DQ2 (trans):
DQA1*05:05/DQB1*02:02 and DQA1*02:01/ DQB1*03:01

SM negative, symptoms suggestive of CD and genetic risk of CD:HLA-DQ2 trans (high risk) and negative to perform biopsy is suggested gluten-free diet(GFD).

After 2 months, he improved psychically and physically, remaining asymptomatic, improving sarcoidosis lesions. After one year GFD, gastroscopic control:IELs 33% (Marsh 1), probably as a consequence of transgressions.

Family study of the four children. Two of them present symptoms similar to the father and genetic study HLA-DQ2.2(low risk), MS negative. They start GFD, disappearing symptoms, do not have a biopsy.

Conclusion

The realization of a genetic study in seronegative adult CD can be a powerful tool if the patient refuses to perform duodenal biopsy. In patients with suggestive symptoms, SM negative and without biopsy, CD is almost safely excluded in genetically nonsusceptible patients (High Negative Predictive Value). The HLA study would prevent future CD controls in patients who are not susceptible.

AUTO1-0492
CELIAC DISEASE AND AUTOIMMUNITY

FREE LIGHT CHAINS AS POTENTIAL INDICATORS OF INTESTINAL MUCOSA NORMALIZATION IN CELIAC DISEASE PATIENTS UNDER GLUTEN FREE DIET

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Background

Celiac disease(CD) is a chronic immune-mediated small intestinal enteropathy, triggered by exposure to dietary gluten in genetically predisposed individuals and frequently diagnosed during childhood. Augmented levels of serum free light chains(sFLC), κ+λ, have been associated with auto-immune conditions making it a potential biomarker for CD diagnosis and response assessment after initiation of the gluten-free diet(GFD). We seek to assess the utility of sFLC levels in the management of CD patients.

Method

Serum samples from 165 CD patients at diagnosis, and 21 samples at 6 months post-GFD initiation. Control group:52 patients with initial suspicion of CD later discarded. Serum tests: antibodies IgA anti-transglutaminase(TG2) and anti-endomysial (Menarini diagnostics), and sFLC (Freelite®)

Results

At diagnosis, median levels of κ+λ sFLC significantly higher in CD patients vs control group (30.2mg/L vs 18.0mg/L, $p<0.0001$, Fig.1). Additionally, a significant decrease of summated sFLC levels was observed at 6 months post GFD initiation(33.6mg/L vs 19.3mg/L, $p=0.0016$, Fig.1): median decrease of 1.5 fold (range: 0.9-3.6). In fact, at 6months post-GFD initiation, the levels of sFLC are equivalent to those of the control group (18mg/L vs 19.3mg/L, $p=0.28$). ROC analysis resulted in an AUC=0.827, $p<0.0001$. Finally, TG2 levels pre- and post-GFD initiation show a reduction.

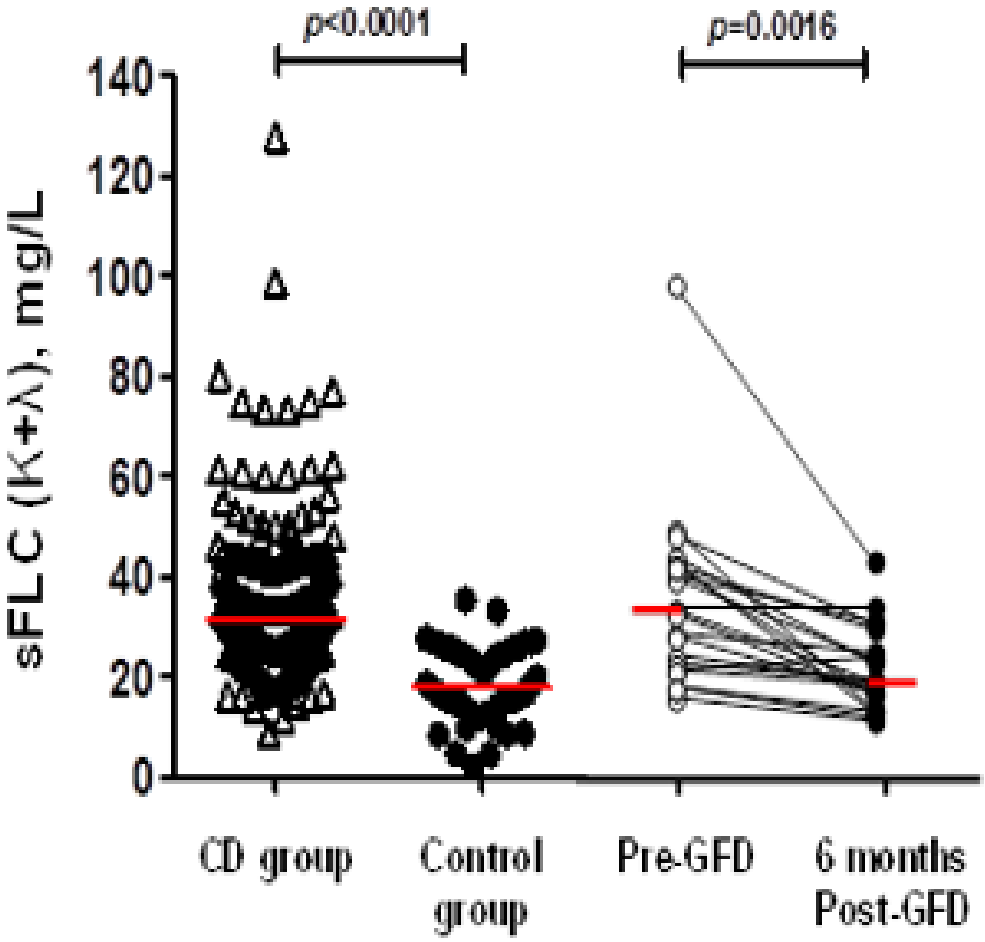

Figure 1. Summated serum free light chain values (sFLC) of 165 CD patients and 52 controls. CD: Celiac disease; GFD: Gluten free diet. The horizontal lines represent median values. Mann-Whitney statistical test.

Conclusion

The significant differences observed between the studied groups shows that sFLC levels (κ+λ) are good indicators of disease response, possibly reflecting normalization of the intestinal mucosa. The decrease of the TG2 values upon GFD initiation supports this hypothesis but validation from patients with available biopsy and larger cohorts are necessary.

AUTO1-0623
CELIAC DISEASE AND AUTOIMMUNITY

NEW SEROLOGICAL MARKERS FOR CELIAC DISEASE: ANTI-NEO-EPITOPE HUMAN AND MICROBIAL TRANSGLUTAMINASES ANTIBODIES

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Background

Microbial transglutaminase (mTg) and human tissue Tg (tTg) complexed to gliadin peptides present neo-epitopes. Antibodies against these complexes are called tTg neo-epitope and mTg neo-epitope. Reliability of antibodies against the non-complexed and complexed forms of both transglutaminases to reflect intestinal damage and to diagnose the pediatric Celiac Disease (PCD) was compared.

Method

95 PCD patients, 99 normal children (NC) and 79 normal adults (NA) were tested using the following ELISAs detecting IgA, IgG or both IgA+IgG combined: tTg (for in house research use only), *AESKULISA*® tTg New Generation (tTg neo-epitope (tTg-neo)), *AESKULISA*® mTg (RUO) and *AESKULISA*® mTg neo-epitope (mTg-neo, RUO). Revised Marsh criteria were used for the degree of intestinal injury.

Results

All anti-mTg-neo and anti-tTg-neo levels were higher ($p<0.001$) compared to the single antigens. tTg-neo IgA and IgG+IgA were higher than mTg-neo IgA and IgA+IgG ($p<0.0001$). The antibody activities reflecting best the increased intestinal damage were: mTg-neo IgA > mTg-neo IgA+IgG > tTg-neo IgG ≥ mTg-neo IgG > tTg-neo IgA > tTg-neo IgA+IgG. Taken together, mTg-neo IgG and tTg-neo IgA and IgA+IgG correlated best with intestinal pathology ($r=0.5633$, $r=0.6165$ & $r= 0.6492$; $p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively).

Conclusion

The complexed forms of both transglutaminases exhibited a higher OD activity and better reflected intestinal damage in PCD, compared to the non-complexed forms. mTg is immunogenic in children with coeliac disease and by complexing to gliadin its immunogenicity and intestinal pathology reflection is enhanced.

AUTO1-0813
CELIAC DISEASE AND AUTOIMMUNITY

ANTI IgA ANTIBODIES DIRECTED AGAINST THE GLIADIN DOCKED MICROBIAL TRANSGLUTAMINASE COMPLEX ARE ELEVATED IN DEPRESSIVE BIPOLAR DISORDER PATIENTS

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Background

Behavioral, depressive and other neuropsychiatric symptoms are observed in celiac disease (CD) and for some of them alleviated by gluten withdrawal, thus reinforcing the gut-brain axis concept. More recently, antibodies directed against the neo-complex of gliadin cross-linked by microbial transglutaminase (mTg-neo) were reported to be immunogenic, reflecting enteric pathology in CD[1].
To explore the prevalence of IgA antibodies directed against the mTg neo-epitope in Depressive bipolar patients.

Method

The presence of IgA anti-mTg neo-epitope antibodies was explored by ELISA (AESKU.DIAGNOSTICS, RUO) in 170 bipolar patients, (52 depression and 118 manic), and compared to 69 healthy controls (HC).

Results

The prevalence of the IgA anti-mTg neo-epitope antibodies was significantly higher in depressive BD patients as compared to HC (12% and 03% % respectively, $p<0.0003$).

Conclusion

IgA mTg neo-epitope antibodies are diagnostic markers in CD[1], representing a new potential environmental inducer linked to the commonly used food additive mTg. The present results open a new aspect relaying mTg neo-epitope antibodies to a psychiatric condition like bipolar depressive condition. The observation put the stage for further exploration of the nutrient-gut-brain axes in psychiatric diseases.

AUTO1-0814
CELIAC DISEASE AND AUTOIMMUNITY

THE PREVALENCE OF ASCA IgA AND IgG ANTIBODIES IS INCREASED IN MANIC BIPOLAR DISORDERED PATIENTS

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Background

Anti-Saccharomyces cerevisiae antibodies (ASCA) are frequent in gastrointestinal inflammatory diseases. Given the concept of gut-brain axis[1] and inflammation induced leaky gut syndrome in psychiatric settings, the prevalence of ASCA is of interest to be analyzed in bipolar disorder.
To study ASCA prevalence in bipolar disorder patients.

Method

IgA+IgG (Check) ASCA were detected by ELISA (*AESKULISA*® Crohn's-Check), in 170 bipolar patients, (52 depression and 118 manic), and compared to 69 healthy controls.

Results

We found that the prevalence of ASCA Check positivity was significantly higher in manic bipolar patients as compared to healthy controls (25% and 13% respectively $p < 0.0023$).

Conclusion

Increased prevalence of ASCA Check antibodies is found in manic phase of bipolar disorder. Environmental processed nutrients, enteric comorbidity or overall enhanced activated immune state can explain this high prevalence.

AUTO1-0400
CELIAC DISEASE AND AUTOIMMUNITY

SEVERE HYPOVITAMINOSIS D IN AUTOIMMUNE DISEASES: A CASE REPORT

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Background

Celiac disease (CD) is an immune-mediated disorder elicited by ingestion of gluten in genetically predisposed subjects. It is characterized by a number of substance deficiencies such as iron, folic acid, and hypocalcemia with impaired absorption of vitamin D. In a number of patients, CD is associated with one or more other autoimmune diseases such as autoimmune thyroiditis (AT).

Method

Case presentation: A 28-year-old woman presenting abdominal pain, diarrhea, fatigue and loss of appetite was admitted to the Hospital "P. Giaccone" in Palermo with suspected CD. Blood tests showed severe hypovitaminosis D (<3 ng/mL), normal serum IgA (414 mg/dL) and IgA anti-transglutaminase (2.6 U) antibodies within normal range. The human leukocyte antigens (HLA) II typing revealed the presence of one beta chain of the heterodimer DQ2 (DQB1*02) in heterozygosity, highlighting a low risk of CD. Laboratory data exclude celiac disease.

Results

Several studies evaluated the role of vitamin D in the pathogenesis of AT, therefore serum thyroid peroxidase, thyroglobulin antibodies (AbTPO, AbTG) and thyroid-stimulating hormone (TSH) were considered. The results (AbTG=747 IU/mL, AbTPO=260 IU/mL, TSH=3.37 IU/L) revealed an autoimmune thyroiditis.

Conclusion

Although hypovitaminosis D is a common finding in CD, a impaired absorption of vitamin D should be considered in the pathogenesis of AT, exspecially when laboratory data and HLA genetic typing esclude CD. This case report evidence the necessity of screening for AT in subjects with hypovitaminosis D, also with clinical signs suggestive of celiac disease.

References: Dohee K. The Role of Vitamin D in Thyroid Diseases.Int. J. Mol. Sci. 2017, 18(9), 1949.

AUTO1-0998
CELIAC DISEASE AND AUTOIMMUNITY

CELIAC DISEASE (CD) IN SELECTIVE IgA DEFICIENCY (sIgAd), STILL CD AND YET SO DIFFERENT

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Background

Total selective IgA deficiency (sIgAd) poses a risk for CD

Method

All total sIgAd who had been tested for CD (IgG tTG, IgG DGP and IgG Endomisyum) from Dec. 2012 to Aug. 2017 were retrospectively reviewed. sIgAd with one or plus IgG positive antibody were included. When available, two assays: INOVA® and Bioplex® were evaluated. A matched IgA-CD control cohort was randomly selected.

Results

29 patients were included. 26/29 CD (17/26 group A: *CD newly-diagnosed*. 9/26 group B: *CD follow-up)*. 3/29 had isolated IgG DGP and were not CD.

In group A at diagnosis 25% were IgG DGP negative. Mean pre-GFD IgG tTG levels were higher by Bioplex® (>17 xULN -Times the Upper Limit of Normality- vs. 7xULN by INOVA®).

After 5 months (±3) of GFD no reduction of IgG tTG was observed by Bioplex®, 20% by INOVA®. Among controls, IgA tTG by Bioplex® showed 60% reduction by this time. When tested simultaneously, IgG tTG showed higher values by Bioplex® (mean 65 xULN higher) compared to INOVA®, with moderate correlation (r=0.6651).

In GFD-adherent at long-term follow-up (26 months) IgG tTG remained positive in >70%, displaying higher values by Bioplex® (13 xULN vs. 2.5 xULN INOVA®).

Conclusion

Our results suggest the importance of a screening strategy based on IgG tTG in sIgAd. This study demonstrates the lower rate of antibody clearance with long-term persistent antibodies despite GFD. Striking differences in antibody levels by two alternative methods might lead to misinterpretations on follow-up. In line with EPSGHAN recommendations, levels associated to villous atrophy are assay-dependant also among sIgACD.

AUTO1-0526
CELIAC DISEASE AND AUTOIMMUNITY

CLINICAL EVALUATION AND METHOD COMPARISON OF NOVEL ASSAYS FOR THE DETECTION OF ANTIBODIES ASSOCIATED WITH CELIAC DISEASE

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Background

Antibodies to tissue transglutaminase (tTG) and deamidated gliadin peptide (DGP) are important factors in diagnosis of celiac disease (CD). Increased anti-tTG IgA titers can be especially important as suggested by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), where a titer 10 times the upper limit of normal may consider foregoing invasive intestinal biopsy in diagnosis of CD. Recently, novel assays have been developed which allow for the detection of antibodies to tTG, DGP, and gliadin. This study aimed to compare the performance of the novel assays with reference methods using clinically characterized samples.

Method

A total of 1157 samples were included in the study, consisting of 135 samples from CD patients, and 1022 samples from patients with various other diseases. All samples were tested by novel bead based immunoassays. Additionally, all CD samples and many control samples were tested in parallel using chemiluminescent (QUANTA Flash tTG and DGP, Inova, USA) and ELISA (QUANTA Lite Gliadin, Inova, USA) based assays currently on the market. Qualitative correlations were calculated and clinical performance was assessed for each of the three analytes.

Results

The results derived from the clinical evaluation and the method comparisons are summarized in the tables below.

Table 1 – Clinical Analysis of the novel assays using all samples (N=1157).

Analyte	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95% CI)	LR- (95% CI)	Odds Ratio (95% CI)	Youden's Index	AUC (95% CI)
tTG IgA	94.1% (88.7-97.0%)	99.3% (98.6-99.7%)	137.3 (66.8-283.5)	0.06 (0.03-0.11)	2301.9 (829.3-6389.0)	0.934	0.998 (0.995-1.001)
DGP IgA	66.7% (58.4-74.1%)	98.6% (97.7-99.2%)	48.7 (28.8-82.6	0.34 (0.26-0.42)	144.0 (76.5-270.9)	0.653	0.957 (0.935-0.978)
tTG IgG	61.5% (53.1-69.3%)	99.9% (99.4-100.0%)	628.3 (111.0-3570.6)	0.39 (0.31-0.47)	1629.7 (279.4-9458.0	0.614	0.962 (0.942-0.982)
DGP IgG	77.0% (69.3-83.3%)	98.4% (97.5-99.0%)	49.2 (30.2-80.4)	0.23 (0.17-0.31)	210.9 (112.0-397.3)	0.755	0.977 (0.966-0.988)
Gliadin IgA	68.1% (59.9-75.4%)	90.7% (88.8-92.3%)	7.3 (5.9-9.1)	0.35 (0.27-0.44)	20.9 (13.7-31.7)	0.589	0.908 (0.882-0.934)
Gliadin IgG	64.4% (56.1-72.0%)	90.9% (89.0-92.5%)	7.1 (5.6-8.9)	0.39 (0.31-0.48)	18.1 (12.0-27.3)	0.553	0.904 (0.876-0.931)

Table 2 – Method comparison and clinical analysis using only samples tested by both methods.

Analyte	NPA (95% CI)	PPA (95% CI)	TPA (95% CI)	*Kappa* (95% CI)	Sensitivity (95% CI) New Method Reference Method	Specificity (95% CI) New Method Reference Method
tTG IgA (n=377)	98.4% (96.0-99.4%)	99.2% (95.6-99.9%)	98.7% (96.9-99.4%)	0.97 (0.94-1.00	94.1% (88.7-97.0%) 91.1% (85.1-94.8%)	99.6% (97.7-99.9%) 99.2% (97.0-99.8%)
DGP IgA (n=377)	98.2% (96.0-99.2%)	94.6% (87.9-97.7%)	97.3% (95.2-98.6%)	0.93 (0.88-0.97)	66.7% (58.4-74.1%) 66.7% (58.4-74.1%)	99.2% (97.0-99.8%) 99.2% (97.0-99.8%)
tTG IgG (n=377)	99.0% (97.0-99.7%)	96.4% (89.9-98.8%)	98.4% (96.6-99.3%)	0.95 (0.92-0.99)	61.5% (53.1-69.3%) 59.3% (50.8-67.2%)	100% (98.4-100%) 98.8% (96.4-99.6%)
DGP IgG (n=377)	97.4% (94.8-98.8%)	98.1% (93.2-99.5%)	97.6% (95.5-98.7%)	0.94 (0.90-0.98)	77.0% (69.3-83.3%) 75.6% (67.7-82.0%)	98.3% (95.8-99.4%) 99.6% (97.7-99.9%)
Gliadin IgA (n=473)	91.4% (88.2-93.9%)	97.0% (91.5-99.0%)	92.6% (89.9-94.6%)	0.80 (0.73-0.86)	67.2% (58.7-74.6%) 55.0% (46.4-63.2%)	88.3% (84.5-91.3%) 92.1% (88.8-94.5%)
Gliadin IgG (n=472)	92.7% (89.6-94.9%)	94.5% (87.8-97.6%	93.0% (90.3-95.0%)	0.80 (0.73-0.86)	64.1% (55.6-71.8%) 56.5% (47.9-64.7%)	91.2% (87.7-93.8%) 95.0% (92.2-96.9%)

Conclusion

Our data show excellent agreement between the results obtained using the assays and the reference methods. Additionally, all analytes showed excellent clinical performance.

AUTO1-0804
CELIAC DISEASE AND AUTOIMMUNITY

SENSITIVITY AND SPECIFICITY OF ANTI-CD74 AUTOANTIBODIES IN EARLY AXIAL SPONDYLOARTHRITIS

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Background

Antibodies against CD74 have been shown to be present in 2/3 of patients with long established axial spondyloarthritis (axSpA). Aims were to explore sensitivity and specificity of anti-CD74 and HLA-B27 in patients with axSpA of recent onset.

Method

205, 18-45y patients suffering from chronic inflammatory back pain (IBP), were compared to 100 blood donors. Ankylosing spondylitis, additional inflammatory rheumatic disorders and biologic therapy were excluded. MRI, HLA-B27 and anti-CD74 using a CE certified kit of AESKU.Diagnostic (Wendelsheim, Germany) were performed blindly. All patients fulfilled ASAS criteria.

Results

Complete data sets are currently available of 122 patients (mean age 29 years, mean duration of IBP 13 months, 56% male). Sacroiliitis and HLA-B27 were diagnosed in 67 %, 69%, respectively. 23 patients fulfilled the ASAS criteria of axSpA by the imaging arm only, 59 by both the imaging and clinical arm and 22 by the clinical arm only. The sensitivities of IgA anti-CD74, IgG anti-CD74 and HLA-B27 were 64.6%, 24.4% and 75% in the axSpA patients fulfilling the imaging arm, 65.4%, 23.1% and 80.7% in the patients fulfilling ASAS criteria, and 3%, 5% and 8% in the blood donors. The likelihood ratios are 21.5 (IgA anti-CD74), 4.9 (IgG anti-CD74) and 9.4 (HLA-B27) when considering the patients fulfilling the imaging arm, and 21.8 (IgA anti-CD74), 4.6 (IgG anti-CD74) and 10.1 (HLA-B27) when considering all patients fulfilling ASAS criteria.

Conclusion

In view of the high likelihood ratio, IgA anti-CD74 is a useful addition to our diagnostic tools for early axSpA.

AUTO1-0458
CELIAC DISEASE AND AUTOIMMUNITY

HLA-DQ TYPING IN CELIAC DISEASE DIAGNOSTIC

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Background

Celiac disease is an immune-mediated chronic disorder whose appearance is due to a combination of genetic (HLA) and environmental (gluten) factors. ESPGHAN focus the crucial role of serological tests and the detection of HLA DQ2/DQ8 to spare biopsies with serum tTG IgA levels ≥10 times upper limit of normal , particularly in children.

Method

We considered this impact during the period 1.4.2016-1.4.2017 in Modena and Parma Diagnostic Department, where the search is made by using *XeliGen RT (Eurospital)* **,** by identifying major HLA genotypes, allowing us to define the "HLA-related risk" of developing celiac disease.

Results

566 typed subjects and 127 respectively in Modena and Parma and 15479 and 6055 tranglutaminase were performed respectively in Modena and Parma. In Modena DQ2 positives were 246 (43%) , DQ8 positives were 59 (10.4%), DQ2/DQ8 were 22 (3.88%) . In Parma DQ2 positives were 65 (51.18%) , DQ8 positives were 11 (8.66 %) , DQ2/DQ8 were 3 (2.36%). We found 245 DQA1*05 (61.6 %) in Modena and 94 (74,0 %) in Parma. Those who had DQB1*02 were 306 (54,06 %) in Modena and 81 (63.77%) in Parma.

Conclusion

The key role of HLA –DQ typing in the diagnosis of CD is to exclude the disease . Those without HLA DQ2 or DQ8 are unlikely to have CD because the sensitivity of HLA testing is high. Our labs must face the challenge of HLA-DQ in terms of numbers and of increasing trend, must analyze own data and monitor frequencies.

AUTO1-0359
CELIAC DISEASE AND AUTOIMMUNITY

EFFECTS OF GLUTEN FREE DIET ON ADULTS WITH CELIAC DISEASE

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Background

Celiac disease (CD) is one of the most common causes of chronic malabsorption with the consequent alteration of micronutrient absorption, such as liposoluble vitamins, iron and B_{12} and folic acid. The only accepted treatment is lifelong adherence to a gluten-free diet (GFD). The **aims** of this study were to identify factors that are independently correlated with GFD adherence, to evaluate the levels of micronutrients and the degree of adherence.

Method

Adults diagnosed with biopsy-confirmed CD participated in this study and followed by completion of two questionnaires and had blood drawn for IgA and IgG anti tissue transglutaminase (tTG) antibody titer, immunoglobulin A (IgA) level and micronutrients concentration.

Results

Twenty eight patients participated; the mean age was 41.7 +/- 13.1 years and 47 % of participants were found to adhere well to a GFD, registered as autoperception and 84% answered that they had positive symptoms when eating gluten. Half of the population felt depressed and 64% of them said that this feeling negatively influenced on their adherence behavior. No significances differences were found in the serum concentration of folate, magnesium, iron and vitamine B12 between both groups ($p>0.05$). The degree of adherence to GFD was poor predictor of low levels of micronutrients (RR: 0.76; 95% CI: 0.38- 1.51). Almost 33 % of the group of low adherence results in positive serum antitransglutaminase IgA.

Conclusion

In **conclusion**, the adherence to diet was associated with some factors but not with level of micronutrients. The presence of antibodies was independent of the perception of self-adherence.

AUTO1-0192
CELIAC DISEASE AND AUTOIMMUNITY

MEASUREMENT OF FECAL GLUTEN PEPTIDES IN MONITORING GLUTEN-FREE DIET IN CELIAC DISEASE PATIENTS

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Background

None of the methods currently used to evaluate gluten free diet (GFD) compliance in celiac subjects offer an accurate measure of the patient's adherence to the diet. Recently, an immunoenzymatic test to detect gluten immunogenic peptides (GIP) in feces, as a trace of gluten consumption in the previous 2-7 days, has been developed.
We evaluated the performance of this new test (iVYLISA, GIP-S, Biomedal SL, Spain) on the Chorus automated instrument (Diesse, Italy), which is specifically designed to perform ELISA test by ready-to-use single test devices, and compared results with the same test performed manually.

Method

16 GFD-treated celiac patients and 21 healthy controls on gluten containing diet were recruited and instructed to collect a stool sample in a dedicated device. 0.2-0.5 g of stools were then diluted in 9 ml/g extraction solution and incubated for 60 minutes at 50 °C. After extraction, the concentration of GIP in stools was analyzed using the iVYLISA GIP-S kit, both manually and by the Chorus instrument.

Results

No significant difference (p=0.314; Wilcoxon) was found in GIP concentration between the manual and the automated method. In the control group, GIP concentrations varied depending on gluten consumption. Among the 16 celiac patients, four had detectable GIP levels in stools. Association was found between fecal GIP results and dietary compliance defined on the basis of clinical evaluation and celiac disease serology markers.

Conclusion

The iVYLISA GIP-S test represents a promising tool to assess the compliance to GFD and it can be easily automated with the Chorus instrument.

AUTO1-0196
CELIAC DISEASE AND AUTOIMMUNITY

EVALUATION OF ADHERENCE TO GLUTEN-FREE DIET MEASURING GLUTEN PEPTIDES IN URINE AND STOOLS OF CELIAC PATIENTS

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Background

Assessing adherence to gluten free diet (GFD) in celiac subjects is difficult as patient's interview is often unreliable and because celiac-specific antibodies may persist for weeks or even months in well-complying GFD-treated patients. We have evaluated two novel tests for the detection of gluten immunogenic peptides (GIP) in feces (by the immunoenzymatic iVYLISA GIP-S assay) and in urine (by the immuno-chromatographic iVYCHECK GIP Urine assay) (Biomedal SL, Spain) and compared results obtained in samples from the two different sources.

Method

15 celiac patients on GFD and 21 healthy controls on gluten containing diet were recruited and instructed to collect a stool and an urine sample on the same day. After extraction, the concentration of GIP in stools and in urine was measured using the iVYLISA GIP-S and the iVYCHECK GIP Urine method, respectively.

Results

All controls resulted positive in both GIP tests. In the celiac group, GIP were present in stool in two patients at a concentration of 210 ng/g and 167 ng/g (cut-off 0.156), while the corresponding urine were negative; another subject had detectable GIP both in stools and urine.

Conclusion

Detection of GIP in stools by the iVYLISA GIP-S test seems to be more sensitive than the test performed on contextual urinary samples and represents a quantitative and objective tool to assess effective compliance to GFD.

AUTO1-0497
CELIAC DISEASE AND AUTOIMMUNITY

BIOPLEX 2200 (BP) ACCURACY IN THE APPLICATION OF ESPGHAN GUIDELINES 2012 (DIAGNOSIS OF CELIAC DISEASE WITHOUT BIOPSY)

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Background

The aim of this study is to evaluate the application of the ESPGHAN guidelines 2012 (diagnosis of celiac disease without biopsy) with the BP anti-tissue transglutaminase IgA (TTG) assay.

Method

229 serum samples of adult and pediatric patients who underwent oesophagogastroduodenoscopy between April 2016 and October 2017 at Papa Giovanni XXIII Hospital were collected. TTG assay was run on BP. Results were analyzed to determine correlation to biopsy and final diagnosis of CD

Results

At the recommended cut-off (15 U/ml), TTG sensitivity and specificity were 97.9% and 100%, respectively, *vs* the diagnosis of CD. Correlation of values at 10X and 15X cut-off to the presence of histological damage suggestive for CD (Marsh > 2) was studied. A value of 150 U/ml (10X) did not show sufficient correlation because positive predictive value (PPV) was < 98%. A value of 225 U/ml (15X) showed a PPV close to 98%, so it may be the suitable cut off for the application of new ESPGHAN guidelines for the diagnosis of CD without biopsy.

Conclusion

Overall, TTG assay shows excellent sensitivity and specificity with respect to diagnosis of CD. To apply the ESPGHAN guidelines for CD diagnosis without biopsy on BP, a cut off of 10X is probably inadequate, as recently described for a similar method* that is also different from immunoenzymatic or fluoroimmunometric assays. A cut off of 15X may be preferable, but further data are needed due to the low number of samples evaluated.

**Previtali G et all., J Pediatr Gastroenterol Nutr. 2017 Oct 6*

AUTO1-0591
CELIAC DISEASE AND AUTOIMMUNITY

GUILEFUL GLUTEN

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Background

Auto-immune nutrition-responsive ataxias are specific and treatable causes in children. We present an instructive case report of the peculiar gluten ataxia.

Method

A 11-year aged girl is admitted for a second episode of acute ataxia. She had only dynamic ataxia with no MRI detected abnormlities in the cerebellum.
She also suffers from chronic diarrhea since several years
Diagnosis of celiac disease with gluten ataxia was supected ; positive serology and flat intestinal mucosa lead to put the teenager on gluten free diet and she has no more presented such ataxias.

Results

Among the large pannel of childhood , few etiologies may have dietary or biochemical therapies. The gluten ataxia is one of the commonest neurological manifestations of gluten-related disorders : prevalence was estimated at 15% amongst all ataxias and 40% of all idiopathic sporadic ataxias ; its diagnosis should be confirmed by the prsence of anti-gliadin antibodies.

Conclusion

Nutritional forms of ataxia should be investigated in pediatric population at first line option as it dramatically respond to dietary adjustment.
Gluten ataxia is also a particular autoimmune ,probably linked to transglutaminase 6, and is a treatable form among the expending spectrum of gluten-related disorders

AUTO1-0654
CELIAC DISEASE AND AUTOIMMUNITY

INTRACELLULAR LOCALIZATION OF MICROBIAL TRANSGLUTAMINASE AND ITS INFLUENCE ON THE TRANSPORT OF GLIADIN WITHIN HUMAN DUODENAL EPITHELIUM

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Background

One central feature of celiac disease (CD) is the infiltration of duodenal epithelium by cytotoxic lymphocytes, representing the effector cells of cross presentation (XPT). As a prerequisite for XPT, exogenous antigens are transported into the endoplasmic reticulum (ER), where they are loaded on MHC class I molecules. Another factor in CD pathogenesis might be the food technological additive microbial transglutaminase (mTG), sharing enzymatic and antigenic properties of human tissue transglutaminase (TG2), the autoantigen in CD. We hypothesized that mTG and gliadin are taken up and transported into the ER of enterocytes, indicating XPT.

Method

Apical incubation of duodenal biopsies from CD patients and non-CD patients (NCD) was performed with mTG alone or simultaneously with a pepsin/trypsin digest of gliadin. Evaluation was done using electron microscopy immunogold-labeled antibodies against mTG, gliadin and protein disulfide isomerase as ER marker for visualization.

Results

The amount of mTG and gliadin within the ER of enterocytes exceeded the background label (BL) significantly (mTG: 7.9 ± 4.7% (mean ± SD) vs median: 1% (IQR: 2); $p < 0.0001$; gliadin: 7.3 ± 3.8% (mean ± SD) vs median: 2% (IQR: 4); $p < 0.0001$). In addition, mTG showed a strong localization within the basolateral membrane and the lamina propria.

Conclusion

This study showed that mTG and gliadin are taken up and transported into the ER of enterocytes, a prerequisite for cross presentation. mTG might be an issue in CD either as a food antigen or as an active enzyme released by bacterial species within the intestinal microbiota.

AUTO1-0678
CELIAC DISEASE AND AUTOIMMUNITY

THE BIOPLEX 2200 CELIAC ASSAYS DEMONSTRATE HIGHER CLINICAL SENSITIVITY THAN THERMOFISHER ELIA CELIAC ASSAYS

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Background

Celiac disease (CD) is an immune-mediated enteropathy triggered in genetically susceptible individuals by ingestion of foods containing gluten. Serology testing plays a primary role in celiac disease diagnosis. The anti-tissue transglutaminase IgA (tTG IgA) assay is the primary assay used for screening for celiac disease. The anti-deamidated gliadin peptide IgA assay (DGP IgA) is a secondary assay which may also be used. The IgG-based assays for tTG & DGP are recommended in the case of IgA deficiency.

The purpose of this study was to compare the performance of the BioPlex 2200 Celiac assays to the ThermoFisher EliA Celiac assays in clinically characterized celiac disease samples.

Method

A total of 116 samples from diagnosed celiac disease patients were tested on the Bio-Rad Laboratories BioPlex 2200 System and the ThermoFisher Phadia 250 System. BioPlex Celiac assay results (tTg IgA/IgG and DGP IgA/IgG) were compared directly to EliA Celiac assay results (tTgIgA/IgG and DGP IgA/IgG).

Results

Sensitivities for the BioPlex and EliA Celiac assays ranged from 51.3 – 92.6% and 27.8 – 80.9% respectively. Positive agreement between BioPlex Celiac assays and Phadia EliA Celiac assays ranged from 92.9 – 100%. Good qualitative agreement was found between the BioPlex and EliA tTG IgA assays.

Conclusion

Overall, the BioPlex 2200 assays showed greater sensitivity for celiac disease in comparison to the EliA assays.

AUTO1-0946
CELIAC DISEASE AND AUTOIMMUNITY

THE BIOPLEX 2200 CELIAC TTG IGA DEMONSTRATES HIGHER CLINICAL SENSITIVITY THAN INOVA BIO-FLASH CELIAC TTG IGA

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Background

Celiac disease (CD) is one of the most common, under diagnosed, treatable lifelong disorders in western countries. The estimated prevalence is around 1% of the general population and average time to diagnosis is 6-10 years. International guidelines recognize anti-tissue transglutaminase immunoglobulin A (tTG IgA) as the first-line serology test to run in a laboratory cascade for celiac diagnosis in patients over the age of 2 years. The IgG-based assays for tTG & deamidated gliadin peptide (DGP) are recommended in the case of IgA deficiency.

Objective

The purpose of this study was to compare the clinical sensitivity of Bio-Rad BioPlex 2200 Celiac tTG IgA to Inova Diagnostics BIO-FLASH Celiac tTG IgA in clinically characterized celiac disease samples.

Method

A total of 116 samples from diagnosed celiac disease patients were tested on the BioPlex 2200 System and on the BIO-FLASH System. BioPlex 2200 Celiac tTG IgA assay results were compared directly to BIO-FLASH Celiac tTG IgA assay results.

Results

Clinical sensitivity was 92.2% for the BioPlex 2200 Celiac tTG IgA and 84.5% for BIO-FLASH tTG IgA respectively. Positive agreement between BioPlex 2200 tTG IgA and BIO-FLASH tTG IgA was 95.9%

Conclusion

Use of the BioPlex 2200 Celiac tTG IgA assay showed greater sensitivity for celiac disease in comparison to the BIO-FLASH Celiac tTG IgA assay.

AUTO1-0319
CELIAC DISEASE AND AUTOIMMUNITY

PREVALENCE OF CELIAC DISEASE IN ADOLESCENTS USING TISSUE TRANSGLUTAMINASE IGA AS SCREENING TEST – A PORTUGESE MULTICENTER STUDY

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Background

The prevalence of celiac disease (CD) is largely unknown in Portugal. The prevalence in the Portuguese region of Braga was estimated to 1:134 95%CI[1:500-1:53] (1.). The primary objective of the study was to investigate the national prevalence of celiac disease in adolescents in Portugal using tissue transglutaminase (tTG) IgA as screening test. The secondary objective was to determine the prevalence of IgA deficiency.

Method

Briefly were samples from adolescents (14 yrs) from the general population collected over one year from all seven regions in Portugal with a sampling error of £1% (1). All sera were analyzed for tTG (EliA Celikey IgA) and total IgA nephelometry. All individuals with a positive tTG test were referred to a pediatric gastroenterologist.

Results

A total of 1458 subjects were included in the study. Eight were positive for tTG and one with an equivocal response was repeated and found positive. Eight of the potential CD

cases were confirmed and one subject was already diagnosed with CD. Based on the 9 confirmed and 1 potential CD cases, the prevalence was determined to 1:146 95%CI[1:382-1:90]. Fifty-one subjects had deficient IgA levels, 4 total and 47 partial, resulting in a prevalence of 1:35 95% CI[1:45-1:27] for IgA deficiency.

Conclusion

The national prevalence of celiac disease among adolescents in Portugal was estimated to 1:146 (0.68%), and the prevalence of IgA deficiency was estimated to 1:35 (3.5%).

Reference

1. Antunes et al., Acta Med Port, 2006

AUTO1-0984
CELIAC DISEASE AND AUTOIMMUNITY

EXTRACELLULAR VESICLES' microRNA ARE INVOLVED IN CELIAC DISEASE

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Background

Celiac disease (CD) is an autoimmune disorder triggered by gluten in genetically predisposed individuals. Its affects around 1% of the world population and thus far the only treatment available is a gluten-free diet. Diagnosis is based on bowel biopsy and specific autoantibody dosage. Identification of extracellular vesicles' (EVs) cargo from blood has been shown to support diagnosis and prognosis of several diseases. We hypothesized that microRNAs from EV of CD patients are involved in CD pathogenesis. To identify possible biological pathways that could be regulated by EV microRNAs in CD, we performed small RNA sequencing (RNA-seq) on 10 CD patients and 10 controls.

Method

EVs enriched in exosomes were isolated from plasma, further pooled cDNA was quantified by *small RNA-seq*. Mapping and alignment of the sequences were performed using the miRMaster tool, and the differences between patient and control profiles were evaluated on R package DESeq2. To detect potentially relevant pathways, we utilized the Diana tool miRpath v.3.

Results

Four microRNAs differentially expressed between patients and controls were detected: hsa-miR-223-3p (fold change=2.4, p=0.0077), hsa-miR-374b-5p (fold change=4.8, p=0.0077), hsa-miR-99b-3p (fold change=-4.3, p=0.0171) and hsa-miR-197-3p (fold change=3.3, p=0.0419), and 17 pathways regulated by these microRNAs were predicted. Some pathways might be involved in CD pathogenesis, such as fatty acid biosynthesis and metabolism, ECM-receptor interaction, protein processing in endoplasmic reticulum, cell cycle, and adherens junctions.

Conclusion

These results disclosed microRNAs whose predicted targets may be involved in biological pathways related to CD pathogenesis, that should be validated in larger samples and further analyzed in functional experiments.

AUTO1-0418
CELIAC DISEASE AND AUTOIMMUNITY

FAMILIAR PREVALENCE OF CELIAC DISEASE IN A GREEK COHORT

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Background

Celiac Disease (CD) is an immune-mediated chronic inflammatory disorder characterized by a permanent intolerance to gluten, in genetically predisposed individuals. CD affects 1-2% of Caucasoids but it is more common in certain high risk groups, such as family members (FMs) of CD patients (pts). The aim of this study was the evaluation of serologic and genetic markers as screening test in the investigation of familiar CD prevalence, in a Greek cohort.

Method

The study included 29 recently diagnosed CD pts and 101 asymptomatic first-degree FMs. HLA-DQA1*/DQB1* typing by high resolution PCR-SSP techniques, anti-tissue transglutaminase (tTG) by ELISA and anti-endomysial (EMA) autoantibodies (AAbs) by IIF, were performed.

Results

At least one CD predisposing HLA allele was typed in 28/29 (96.5%) pts and 77/101 (76.2%) FMs. Among them 86 (66.1%) were DQ2, 12 (9.2%) DQ8 and 7 (5.3%) DQ2/8 double positive. All pts and 21 FMs were positive in at least one of the tested Aabs (100% tTG and 96% EMA) and all of them but one pt carried a high risk HLA allele. The study revealed 21 new CD cases (4 parents, 10 offsprings, 7 siblings) according to ESPGHAN diagnostic criteria, all possessing both genetic and serological CD markers.

Conclusion

The prevalence of CD among first-degree relatives appears higher (20.8%) than in the general population. The fact that these pts remain undiagnosed may lead to severe complications. Therefore, a screening strategy with HLA genotyping as well as tTG and EMA AAbs serological testing, could be strongly recommended in FMs of CD pts.

AUTO1-0689
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE PRESENCE OF ANTICARDIOLIPIN ANTIBODIES IN PATIENTS WITH DEMENTIA

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Background

Growing evidences are supporting towards the involvement of antiphospholipid antibodies [aPLs; lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2-glycoprotein I (anti-β2-GPI) antibodies] in various neurological manifestations including migraine, epilepsy and dementia in presence or absence of autoimmune diseases such as antiphospholipid syndrome or systemic lupus erythematosus. The aim of this systematic review and meta-analysis was to assess the presence of aPLs in patients with dementia without suffering from autoimmune diseases.

Method

Electronic databases (e.g., PubMed, Web of Science, Scopus, ScienceDirect and Google Scholar) were searched without any year or language restrictions.

Results

Based on the inclusion criteria, nine prospective case-control studies were included involving 372 dementia patients and 337 controls. The study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects models. We observed the prevalence of aCL in dementia was higher (32.80%) than that of controls (9.50%) and significant presence of aCL antibodies was detected in demented patients compared to controls (OR: 4.94, 95% CI: 2.66 - 9.16, $p < 0.00001$; $I^2 = 32\%$, $p = 0.16$). Publication bias was not observed from Egger's ($p = 0.081$) and Begg's tests ($p = 0.180$). Based on the study quality assessment using modified Newcastle-Ottawa Scale for case-control studies, seven of nine studies were of high methodological quality scoring ≥ 7 (median value).

Conclusion

In summary, aCL antibodies were significantly present in dementia patients suggesting that aCL antibodies are generated due to the autoimmune-derived effects of dementia or there might be a potential causative role of this autoantibody in dementia pathogenesis.

AUTO1-1024
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

MONOCLONAL GAMMOPATHY OF SIGNIFICANT INCERTO (MGUS) AND AUTOIMMUNE NEUROPATHIES: STUDY IN A GENDER PERSPECTIVE

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Background

The purpose is to understand if there is a correlation between anti-Mag and anti gangliosides in individuals with MGUS.The association between MGUS and chronic inflammatory demyelinating polyneuropathies is about 10%.The polyneuropathies associated with IgM-MGUS have a progressive chronic course. The IgM monoclonal component shows a reactivity towards the MAG in a percentage between 60-90%. The IgG and IgM antigangliosides present in 50% of motor neuropathies and the anti-MAG in individuals with MGUS were assayed.

Method

140 patients, 96 males and 44 females, between 30 and 90 years, starting from the initial 4200 with monoclonal component. They were subjected to the dosage and the typing of the immunoglobulin class, to the dosage of the anti-MAG and to the dosage of the anti-ganglioside IgG and IgM.

Results

37% are positive for the typing of the monoclonal component, of which 58% of the IgG class, 22% of the IgA class and 20% of the IgM class. 15% of patients were positive for anti-MAG antibodies, mostly women, in particular 75% associated with the IgM isotype; 42% were positive for antigangliosides more in men. Anti-GANG-IgG in 85% of men and 15% of women ($p = 0.004$), anti tetrasialoganglioside in males, and anti-trisialoganglioside in females ($p < 0.001$).

Conclusion

There is an association between anti-MAG and anti-gangliosides in subjects MGUS. In the male MGUS, the presence of the anti-gangliosides characterizing the Miller-Fisher syndrome is observed and in the female the chronic ataxic neuropathy.

AUTO1-0566
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

EFFECT OF RAPAMYCIN ON THE MULTIPLE SCLEROSIS, A CLINICAL TRIAL

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Background

Multiple sclerosis (MS) is an autoimmune disease characterize by demyelinating plaque in the central nervous system. The disease has no cure and no recognized definite cause yet. The available therapies are mostly disease modifying. The aim of the present clinical trial was to evaluate the therapeutic effects of rapamycin on the clinical, life quality and radiological aspects of the patients with MS.

Method

In this phase I clinical trial, eight patients with relapsing remitting MS were chosen to be included in the trial. Patients have been received rapamycin (Rapacan, Biocon, India) for six months. The safety of drug on the participants was monitored by checking the hematological and blood biochemical parameters of the patients in days 0, 30, 60, 90, 120, 150 and 180 after initiation of study. Magnetic resonance imaging (MRI) of the brain of the patients has been taken before and after therapy. Patients' expanded disability status scale (EDSS) was also been recorded.

Results

After the therapy was finished, all patients had some degrees of significant reduction in mean plaque area volume (P=0.012, Z= -2.520), and minimum and maximum volume (P=0.012, Z=-2.521) of the plaques. EDSS of 4 (50%) out of 8 patients was decreased after treatment with rapamycin, but was not significantly (P=0.059, Z=-1.89).

Conclusion

This study was the first clinical trial on the effect of rapamycin on multiple sclerosis, which showed promising results for treatment management of the disease. According to the findings, rapamycin is beneficially effective on multiple sclerosis and suggested for therapy of this disease.

AUTO1-0571
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

CENTRAL NERVOUS SYSTEM IMMUNOREACTIVITY IS RELATED TO CLINICAL EXPRESSION DURING BEHCET DISEASE AND IS MORE PRONOUNCED IN NEUROLOGICAL AND OCULAR INVOLVEMENT

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Background

Behçet disease (BD) is a chronic systemic inflammatory affection with uncertain etiology. Autoimmunity seems to play an important role in its physiopathology. In this study, we investigate a putative presence of specific auto-antibodies against the local structures in relations with the clinical expression during BD.

Method

39 patients BD and 15 healthy controls were enrolled in this study. We evaluated the immunoreactivity of patients' sera (n=39) and/or cerebrospinal fluid (CSF, n=7) toward bovine retina and brain by ELISA (soluble extracts) or immunohistochemistry against paraffin-embedded sections. Mann-Witney U test and Spearman test were used for statistical analysis.

Results

Healthy controls' sera did not show any reactivity. Immunostaining with patients' sera was positive against the outer segments of photoreceptors and ganglion cells in retina. Positive cytosolic staining in neurons and sporadic filamentous labeling were observed in brain sections. ELISA results showed positive reaction toward the two extracts in all patients. However, patients with uveitis showed a significant increase in reactivity to retinal and brain extracts ($p<0.05$). There was a significant correlation between reactivity toward the two extracts ($r=0,887$, $p<0,001$). Neurological involvement was characterized by a significant increase in reactivity to brain extract in men ($p=0.009$). Patients' CSF showed a significant correlation between the title of auto-antibodies against brain extract and progressive parenchymal involvement ($r=0,775$, $p<0.05$) or cerebellar syndrome ($r=0,894$, $p<0.01$).

Conclusion

We showed autoantibodies presence in both sera and CSF from patients with BD. The existing correlation with the clinical expression and severity emphasis the important role of autoimmunity in the disease physiopathology.

AUTO1-0109
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

REDUCTION OF EXPERIMENTAL AUTOIMMUNE MYASTHENIA GRAVIS FOLLOWING ORAL ADMINISTRATION OF A SOYBEAN-DERIVED TOLEROGEN

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Background

The difficulties for creating oral tolerance therapies are twofold: practicality and efficacy. Practically, most protein autoantigens will be expensive to manufacture, administer, and may not remain intact following passage through the gastrointestinal tract. Therapeutically, even if some of the protein autoantigens survive to interact with immune cells in the Gut Associated Lymphoid Tissue (GALT), their ability to significantly reduce autoimmune T and B cells responses in humans is unclear. Developing a routine, practical strategy for oral autoantigen therapy is certainly a difficult proposition.

Method

Experimental autoimmune myasthenia gravis (EAMG) can be induced in rats by immunization with an autoantigen, the alpha 1 subunit of the human nicotinic acetylcholine receptor (AChR). In an effort to reduce this induced autoimmune response, we were successful in manufacturing a fusion protein composed of a mucosal targeting sequence and the AChR autoantigen in transgenic soybean seeds. Despite being complex, and requiring trimerization for binding to microfold cells in GALT, this fusion protein could be delivered orally in simple soymilk preparations.

Results

Treatment of rats experiencing EAMG with this oral tolerogen resulted in a significant reduction in peripheral muscle weakness, as well as a reduction in the autoantibody response against AChR. As expected, the administration of these simple soymilk formulations was well tolerated in these animals.

Conclusion

The ability to manufacture complex, functional recombinant proteins, and to formulate an oral tolerance therapy directly from transgenic soybean seeds which are safe, efficacious, and cost effective, illustrate strengths of this platform technology.

AUTO1-0138
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

IMMUNOLOGICAL PROFILE IN BIOPSIES OF PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

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Background

Primary angiitis of the central nervous system (PACNS) is a rare autoimmune disease characterized by the inflammation of central nervous system arteries without compromising any other organs, and without a primary cause. This disease predominately affects medium to small caliber arteries in the brain parenchyma, the spinal cord and the meninges, causing central nervous system (CNS) dysfunction (1). Its pathophysiology is not yet elucidated, but it appears to be mediated by antigen presentation to the T lymphocytes in the arterial wall (2). The aim of this study is to evaluate the immunological profile in two biopsies of patients with primary angiitis of the central nervous system.

Method

We describe a immunological profile in biopsies of primary angiitis of the central nervous system

Results Results: An immunohistochemical study was done in 2 samples, revealing a leukocytic infiltration (CD45+) constituted almost entirely of T lymphocytes (CD3+) with a clearly higher prevalence of CD4+ cells (Figure1), with no evidence of plasmatic cells (CD138 and CD38 markers were negative) and an absence of Treg Lymphocytes (negativity for CD25). Class II HLA expression was detected in 50 % of the cells in both samples (Figure 2).

Figure 1

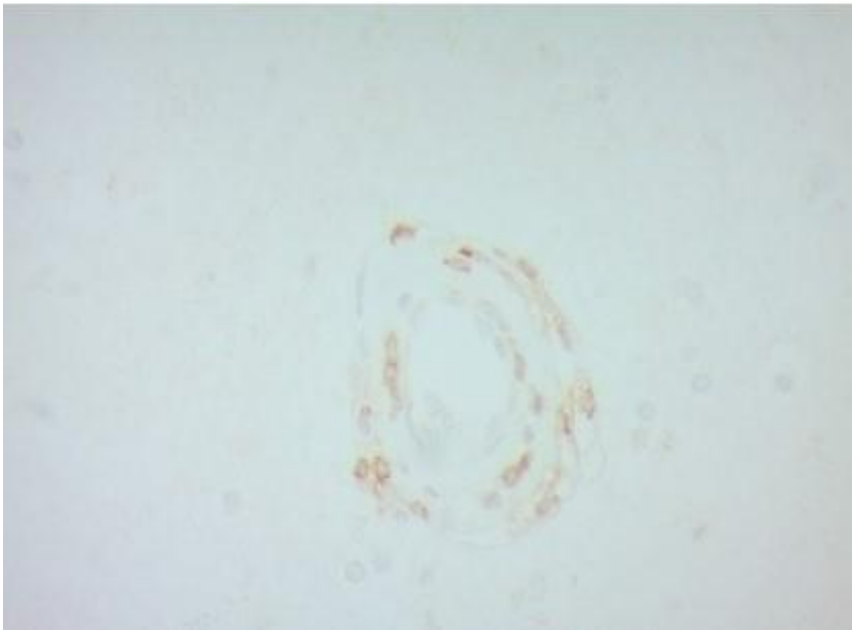
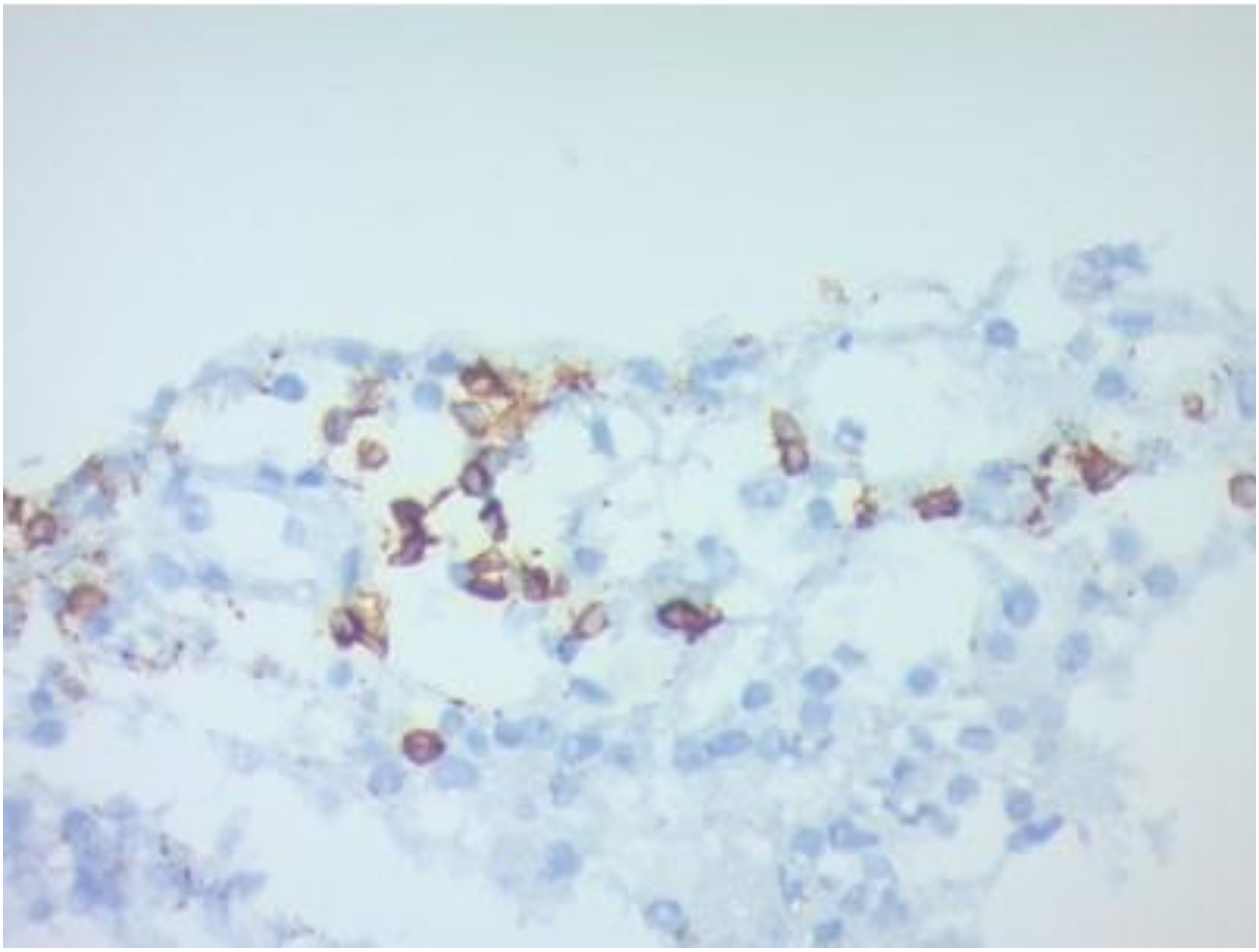


Figure 2



Conclusion

Our study suggests a T lymphocyte (with CD4 predominance) in patients with PACNS. The negligible presence of B lymphocytes and the absence of plasmatic cells implies this is not a humoral immunity mediated entity. Nevertheless, more complex studies are required to understand the pathophysiology of this disease and the cytokine expression pattern.

AUTO1-0647
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

LABORATORY APPROACH TO ANTI-IGLON5 ANTIBODIES IN TWO PATIENTS SUSPECTED OF PARANEOPLASTIC NEUROLOGIC SYNDROME

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Background

Anti-IgLON family member 5 (IgLON5) autoantibodies have been recently described as an important biomarker for early differential diagnosis of autoimmune encephalitis, neurodegenerative diseases and sleep disorders.
Patients with antibodies against IgLON5, a neuronal cell adhesion protein, develop a new neurologic disease with a characteristic sleep disorder, abnormal movements and cognitive decline.
Anti-IgLON5 disease usually has an insidious onset, it´s progressive, irresponsive to immunotherapy and has a high mortality rate.
Anti-IgLON5 autoantibodies can be screened in serum and CSF by indirect immunofluorescence (IFA) on rat cerebellum and confirmed by cell-based assay (CBA) using HEK 293 transfected cells with IgLON5.

Method

We describe two patients suspected of PNS referred to our laboratory for anti-onconeuronal antibodies.
Serum from both patients were tested by IFA on rat cerebellum slides (INOVA) and by immunoblotting (“Paraneoplastic Neurologic Syndromes 12 Ag”, EUROIMMUN).

Results

The results became negative for all the anti-onconeuronal antibodies on blotting but in rat cerebellum we found a strong neuropil pattern which made us suspected of the presence of an antibody against cell membrane surface. We decided to perform a CBA for the most common autoimmune encephalitis antibodies (“Autoimmune mosaic encephalitis 1”, EUROIMMUN) but we couldn’t found any specificity, so we send both samples to a reference laboratory. The results became positive to anti-IgLON5 for both patients.

Conclusion

Due to the heterogeneous clinical presentation, determination of anti-IgLON5 should be considered when a “neuropil pattern” on rat cerebellum is found and antibodies against the most frequent cell surface antibodies are negative.
Anti-IgLON5 disease is most likely underdiagnosed.

AUTO1-1062
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

POST-LUMBAR PUNCTURE HEADACHE AFTER PURSUING UVEITIS ETIOLOGY - A SPHENOPALATINE GANGLION BLOCK REPORT

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Background

Post-lumbar puncture headache (PLPHA) is a very common complication, which occurs 10 to 30% of patients following lumbar puncture. Despite symptom severity and considerable morbidiy, current therapies are often insufficient to treat PLPHA. Sphenopalatine ganglion block is a minimally invasive technique recently studied in PLPHA. A swab embedded in anesthetic is placed on the nasal posterior mucosa just adjacent to the sphenopalatine ganglion. Trans-mucosal anesthesia is provided blocking trigeminal sensitivity, meningeal nociception and parasympathetic meningeal vasodilatation which are central in PLPHA.

Method

Report of a case vignette.

Results

We present a case of a 34 year old man who was admitted to our Immune-mediated disease unity with uveitis. Besides red eye with ocular pain, no other symptoms were reported. Laboratory evaluation including autoimmunity workup and head MRI were unremarkable. A lumbar puncture with a 22 gauge needle was performed. Cerebrospinal fluid was completely normal. He was discharged and referred to autoimmunity and ophthalmology clinics. He was readmitted 48h later with severe postural headache with neck irradiation, nausea and vomiting. No fever was reported and there was no leukocytosis or acute phase reactants rising. He was started on paracetamol, caffeine and intravenous hydration with no improvement. Sphenopalatine ganglion block was performed with lidocaine 5% gel lasting 20 minutes. Headache was relieved after 10 minutes and completely remitted after 1 hour. He was discharged on the next day.

Conclusion

We report a severe case of post-lumbar puncture headache successfully treated with an incredible simple minimally invasive technique: sphenopalatine ganglion block.

AUTO1-0795
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

THE ROLE OF α-SYNUCLEIN-SPECIFIC T CELLS IN PARKINSON'S DISEASE PATHOGENESIS

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Background

The role of inflammation in the pathology of Parkinson's disease (PD) remains elusive. In addition to loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and deposition of hyperphosphorylated α-synuclein (a-syn) aggregates, PD patients sustain persistent inflammation, marked by infiltration of lymphocytes and active microglia, and increased levels of inflammatory cytokines in the periphery. In mouse models for the disease, neuronal death is attenuated in the absence of mature T lymphocytes or major histocompatability complex (MHC) class II protein. Since a-syn is hyperphosphorylated and proteolytically misprocessed in brains of PD patients, neo-antigens of a-synuclein are likely formed. We have shown that peptides derived from a-syn induce T cell responses in PD patients but not healthy controls. In addition, these peptides strongly bind to distinct MHC complexes that are encoded by Human Leukocyte Alleles (HLA), which are over-represented in our PD donors and associated with responding to a-syn neo-epitope. While these findings strongly suggest that PD is in part an autoimmune disorder, analysis in PD patients limits our understanding of how a-syn specific T cells may drive dopaminergic neuron death.

Method

Emulating the experimental autoimmune encephalomyelitis mouse model, we demonstrate that a-syn immunizations produce a-syn specific Th17 T cells in C57BL6/J mice.

Results

We are currently analyzing the effects of a-syn specific T cells in the brain and gut. In addition, the immunizations will be repeated in humanized mice that express an HLA allele overrepresented in PD patients.

Conclusion

This project will determine the role of a-syn T cells in PD pathogenesis.

AUTO1-0618
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

Anti-Serotonin antibodies in Fibromyalgia patients

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Background

Fibromyalgia (FM) is an idiopathic disorder characterized by widespread nonarticular musculoskeletal pain accompanied by fatigue, sleep and memory disorders and mainly affecting women. The etiopathogenesis of FM is still unknown but evidence suggests an inflammatory and autoimmune origin characterized by an autoantibody pattern. Presence of antibodies to serotonin (5-hydroxytrypyamine) has been found in about 70% of German FM patients and appears to be characteristic for this disease. Our aim was to evaluate the presence of antibodies to serotonin in serum of Spanish type I FM patients.

Method

The study included 156 clinically defined FM patients and 153 healthy controls. Sera from patients and control subjects were tested by ELISA against Serotonin, as described by Klein et al. (1992).

Results

Anti-serotonine antibodies were found in 65 % of the patients suffering from FM. Statistically significant difference was found with respect to healthy controls that presented 14% ($Pc<0.05$).

Conclusion

Our data corroborate German results, presence of antibodies to serotonine in FM patients. The diagnostic relevance of these antibodies is supported by the absence of anti-serotonin antibodies in other rheumatic disorders. The association of anti-serotonine antibodies with psychiatric disorders in FM is thought to represent at least partially a dysregulation of the serotonergic neurotransmitter system in the central nervous system. Although these immunological results are still beyond our understanding, they could indicate an autoimmune component of the disease regardless of inflammatory response or alterations of the neuroendrocrine system. Broader studies will be necessary in the future.

AUTO1-0696
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODIES (MOG-IgG) POSITIVE NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMO-SD): A SINGLE INSTITUTION EXPERIENCE

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Background

10-27% of NMO-SD patients diagnosed according to the 2015 International panel on NMO diagnosis are seronegative for aquaporin-4 antibodies(AQP4-IgG).Recent evidence suggests that some of these seronegative NMO-SD patients have antibodies against myelin oligodendrocyte glycoprotein(MOG).In this study,we aimed to describe the epidemiological, clinical,radiological, cerebrospinal fluid,attack status and treatment outcomes of MOG-IgG positive NMO-SD patients.

Method

In this retrospective single center study,all MOG-IgG positive NMO-SD patients were evaluated over the last 5 years.

Results

12 patients(7 male,5 female)were reviewed.Median age of onset was 33 years(range 15-49 years).1 patient was seropositive for both AQP4-IgG and MOG-IgG.1 patient has ITP and SLE.3 out of 12 patients had antibodies against ANA, anti-dsDNA, anti-phospholipid, anticardiolipin, beta-2 glycoprotein.The clinical presentation at onset was, isolated optic neuritis in 7,isolated transvers myelitis in 4 and optic neuritis + transvers myelitis in 1 of 12 patients.7/12 patients had multiphasic course clinically.Oligoclonal bands were absent in 8/12 patients.Median EDSS score was 4.0 and the mean number of attacks were 4,25.1 patient died due to hemolytic crisis secondary to ITP.MRI findings were as follows: supratentorial(n=5),optic nerve(n=5),brainstem(n=5),longitudinally extended transvers myelitis(LETM)(n=9).Acute episodes were treated with intravenous methylprednisolone(n=12),plasma exchange(n=5) and intravenous immunoglobulin(n=1). Azathioprine(n=6), cyclophosphamide(n=2), oral methylprednisolone(n=1), rituximab(n=5), methotrexate(n=1),mycophenolate mofetil(n=1)and eculizumab(n=1) were used for long term treatment.(See Table 1).

TABLE 1– Demographic and Clinical Data of Cases

Age, Gender	Age of Onset	Presenting Symptoms	Optic Neuritis	Transverse Myelitis	Attack Treatment	Long-term Treatment	Antibody Status	Oligoclonal Band	Treatment Response	EDSS
41 y, F	37 y	Right lower extremity paresis	-	3	MPZ, PExc	AZA, ECU	NMO and MOG +	Negative	Partial	5.5
37 y, M	34 y	Right ON	1	-	MPZ	MPZ	MOG +	Negative	Complete	0.0
50 y, M	49 y	Right hemiparesis	-	1	MPZ	CYC	MOG +	Negative	Partial	Exitus due to ITP
36 y, M	15 y	Right ON	10	2	MPZ	AZA	MOG +	Negative	Near complete	2.0
43 y, M	35 y	Left ON	14	-	MPZ, PExc, Ivig	MMF, MTX, CYC, RTX	MOG +	Negative	Partial	4.0
51 y, M	49 y	Right ON	3	1	MPZ	AZA	MOG +	Type 4 Positive	Partial	5.5
34 y, F	32 y	Bilateral ON	1	-	MPZ	AZA	MOG +	Negative	Complete	0.0
18 y, M	18 y	Left ON, paraparesis	1	1	MPZ, PExc	AZA	MOG +	Not available	Partial	6.5
29 y, F	27 y	Paraparesis, urinary incontinence	2	1	MPZ, PExc	AZA, RTX	MOG +	Type 2 positive	Near complete	1.5
22 y, F	22 y	Paraparesis, urinary ret, gaita incont.	1	2	MPZ, PExc	RTX	MOG +	Negative	Partial	5.0
34 y, F	25 y	Right ON	6	-	MPZ	RTX	MOG +	Negative	Near complete	3.0
42 y, M	42 y	Bilateral ON	1	-	MPZ	RTX	MOG +	Not available	Partial	4.0

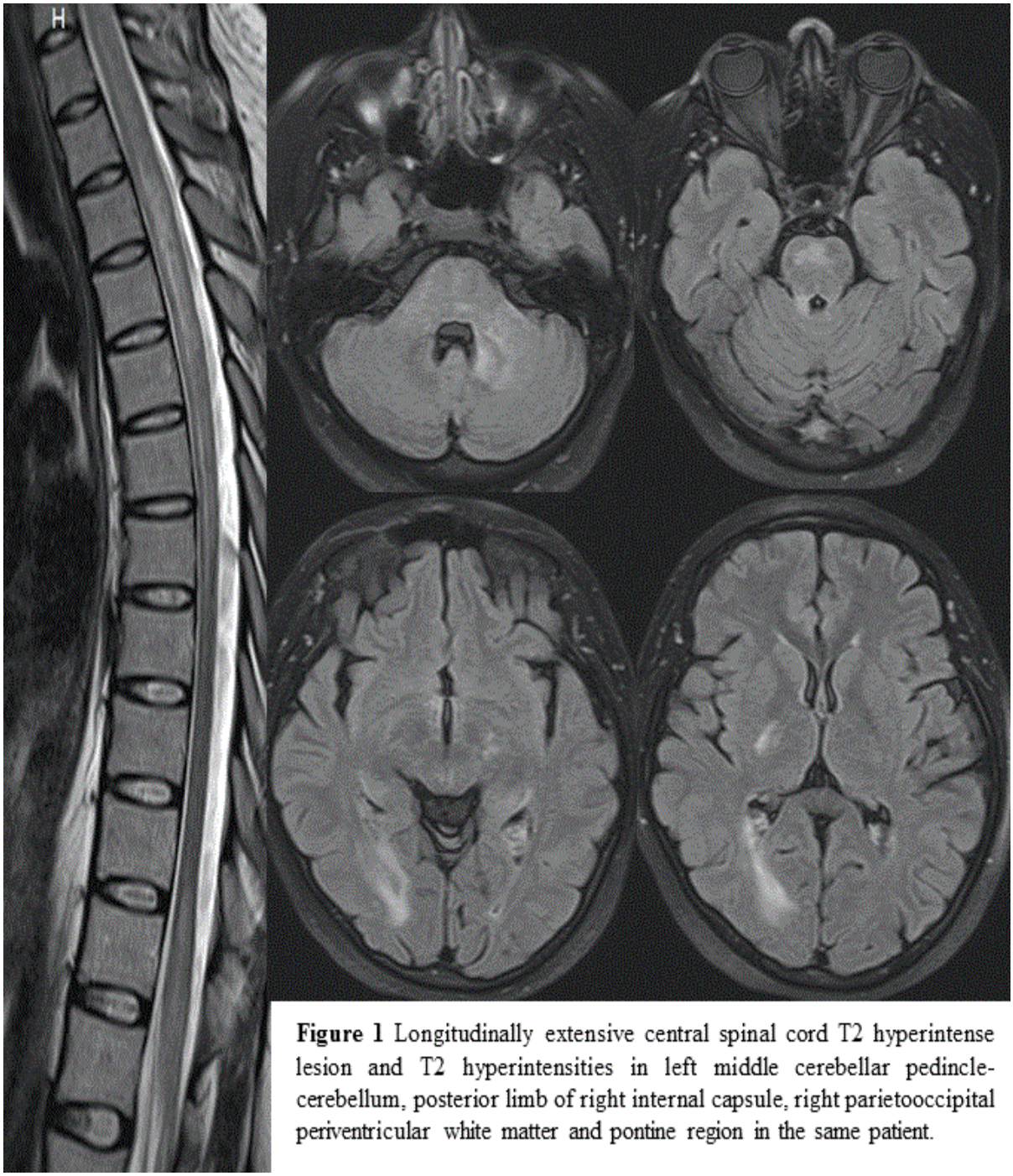

Figure 1 Longitudinally extensive central spinal cord T2 hyperintense lesion and T2 hyperintensities in left middle cerebellar pedincle-cerebellum, posterior limb of right internal capsule, right parietooccipital periventricular white matter and pontine region in the same patient.

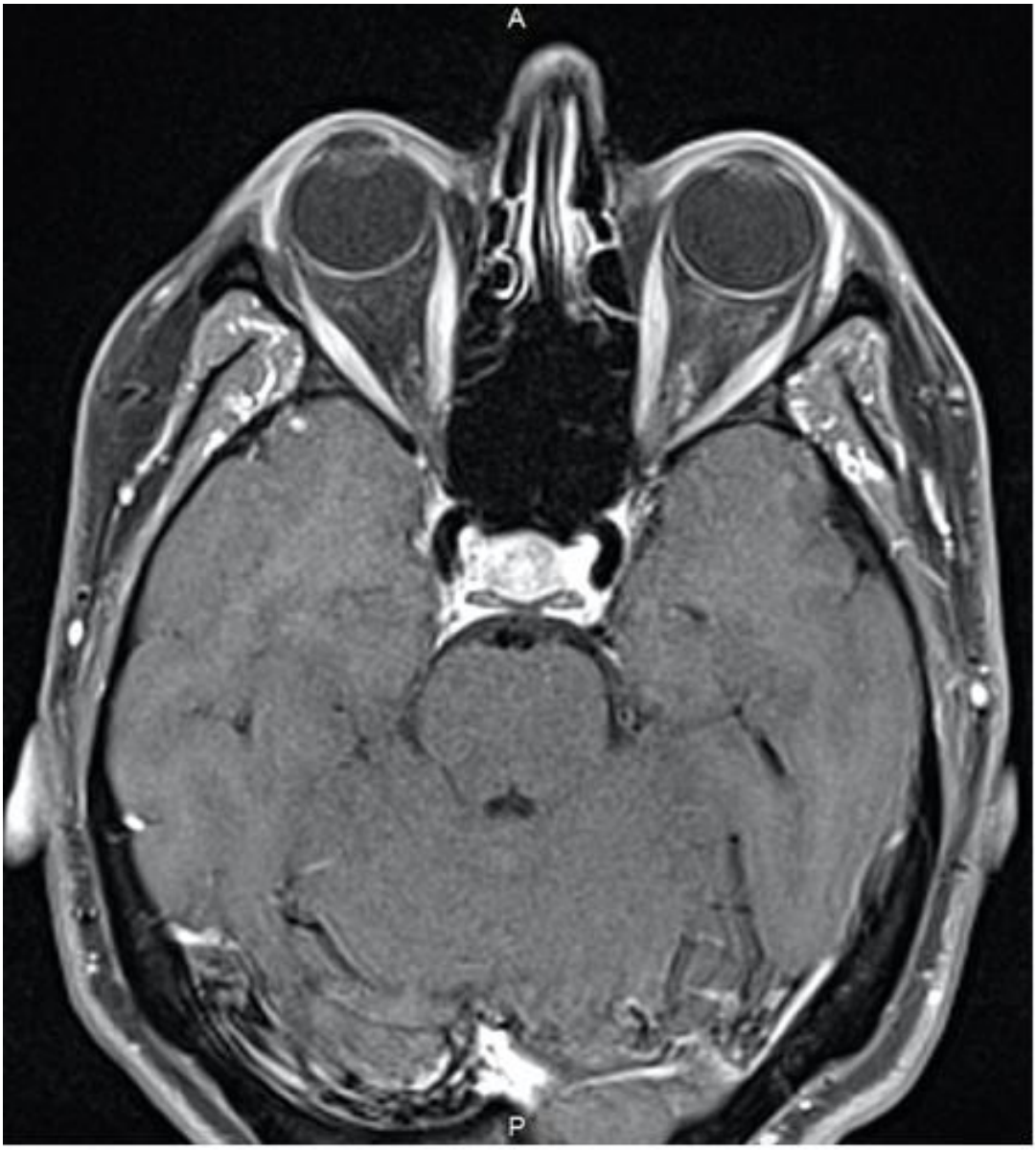

Figure 2 Increased signal intensity in intracanalicular segment of left optic nerve.

Conclusion

MOG antibody-associated NMO-SD reveals a unique clinical,radiological, and therapeutic profile that needs to be clearly defined at onset to conduct appropriate management.MOG-IgG positive ON and myelitis frequently follow a relapsing,severe course and may not have always a favorable outcome.We propose a close follow up and prophylactic long term treatment.

AUTO1-0363
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

MACULAR THICKNESS BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY AS A PREDICTIVE FACTOR FOR RETINAL VASCULITIS IN THE ABSENCE OF CYSTOID MACULAR EDEMA

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Background

To evaluate the significance of central retinal thickness as a predictive factor for underling retinal vasculitis in the absence of cystoid macular edema.

Method

A total 80 patients with at least anterior uveitis and underwent fluorescein angiography (FA) were included. The patients were classified into three groups according to the severity of retinal vasculitis: absent, mild, and severe group. The average macular thickness (MT) in each of the 9 Early Treatment Diabetic Retinopathy Study (ETDRS) areas were obtained by spectral domain optical coherence tomography (SD ODT) and evaluated.

Results

Among 80 patients, 24 patients had no retinal vasculitis and 27 patients did mild retinal vasculitis. 29 patients had severe retinal vasculitis and underwent systemic or intravitreal steroid treatment. At the baseline, the mean central MT was 265.2±27.5㎛ in the absent group, 274.2±19.3㎛ in the mild group, and 310.4±63.6㎛ in the severe group (P=0.001). The mean MT for each sector was significantly different among the three groups in 3 mm diameter (superior, temporal, inferior, and nasal, P<0.001, respectively). It shows similar tendency in the analysis of 6 mm diameter (superior, temporal, inferior, and nasal, P<0.001, respectively).

Conclusion

The mean MT of the 9 ETDRS areas by SD OCT was significantly thicker in the patients with retinal vasculitis than those without on FA. The mean CMT was also significantly thicker in the patients with severe retinal vasculitis than those with mild retinal vasculitis. The MT by SD OCT may be helpful for screening and treatment monitoring of underlying retinal vasculitis.

AUTO1-0360
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

PEDIATRIC TUMEFACTIVE DEMYELINATION; BIOPSY PROVEN PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

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Background

Differential diagnosis of tumefactive demyelinating lesion from other inflammatory brain diseases/neoplasms/abscesses remains challenging on neuroimaging.

Method

Here we report a pediatric case with a mass-like lesion, who was diagnosed primary angiitis of the CNS after biopsy.

Results

A previously well 14-year-old Korean male presented with confused mentality after generalized seizure.

Magnetic resonance imaging(MRI) revealed T2-hyperintense, infiltrating lesion with focal enhancement in the right basal ganglia(BG), thalamus, and periventricular white matter(WM).

Cerebrospinal fluid analysis revealed 79 leukocytes (62% lymphocytes), protein 41.6mg/dl, and negative cultures.

Because of mass-like lesion with extensive surrounding edema, the lesion was thought to be a tumor, and brain biopsy was performed. Pathologic studies revealed a lymphocytic vasculitis.

He was treated with pulse intravenously methylprednisolone for 3 days, followed by a tapering dose of oral prednisolone.

One month after completing prednisolone, he developed generalized seizure again. MRI displayed newly appeared lesion to be of increased signal on T2-weight/Flair images with faint enhancement in the right side anterior BG, caudate nucleus and internal capsule. He was diagnosed with primary angiitis of CNS, and treatment with lower dose of prednisolone and immune-suppressant therapy(azathioprine) was commenced.

He remains well, without seizures 1.6 years after his initial presentation**Conclusion**

Tumefactive demyelinating lesions are uncommon manifestation of demyelinating disease and can pose a diagnositic challenge in patients without a pre-existing diagnosis of multiple sclerosis. It is important that other pathologies such as vasclitis, granuloma, infection and malignancy are excluded. In this case, brain biopsy can be crucial in final diagnosis.

AUTO1-0361
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

DIFFICULTY IN DIFFERENTIAL DIAGNOSIS OF RECURRENT BRAINSTEM SYNDROME; RHOMBENCEPHALITIS OR NEUROMYELITIS OPTICA ?

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Background

Acute brainstem syndrome may be the initial manifestation of various diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), encephalomyelitis.

In the absence of autoantibodies including anti-aquaporin 4 (AQP4) antibody, to confirm a diagnosis is not easy.

Method

Here, we present the case of a 45-year-old man who has not been confirmed diagnosis, but suspected have an autoimmune – mediated encephalitis or CNS vasculitis of unknown etiology.

Results

He was first admitted to our hospital at age 44 due to headache and fever. The patient developed a tingling sensation in the upper extremities and gait disturbance.

He was tentatively diagnosed with neuro-behcet's disease or other vasculitis on the basis of T2 high signal intensity (HIS) lesion with patch Gd-enhancement in the brainstem. (and CSF results)

His serum and CSF samples tested negative for auto antibodies including anti-NMDA receptor antibodies.

Infectious etiology was excluded, ig G index was normal and AQP4 antibodies were negative.

After treatment with oral corticosteroids, there was recovery in the acute phase.

10 months later, he developed dysarthria and dysphagia abruptly. T2/FLAIR MRI images showed a HIS in the both cerebral peduncles to pons.

He showed good recovery with steroid medication and immunosuppressive treatment was started since the recur.

Conclusion

Our patient had common features of both recurrent rhombencephalitis and NMO, illustrating that diagnostic characterization is not easy in spite of current criteria.

Further, repeated investigations, and close observation of clinical course are required to clarify the definite diagnosis in our patient.

AUTO1-0131
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

FAMILIAL ASSOCIATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH AUTOIMMUNE DISEASES

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Background

In the era of genome-wide association studies, familial risks are used to estimate disease heritability and success in gene identification. We wanted to estimate associations of 43 autoimmune and related diseases with attention deficit hyperactivity disorder (ADHD) among parents and offspring.

Method

The availability of a Multigeneration Register in Sweden provides a reliable access to families throughout the last century. The diseases in individual family members were obtained through linkage to the Hospital Discharge Register. Standardize incidence ratios (SIR) were calculated as relative risks for ADHD in family members of affected patients compared to those lacking affected family members.

Results

Among a total of 86,805 patients, 18,320 were diagnosed with family history of autoimmune disorders. ADHD in offspring associated with 14 diseases in first-degree relatives, including ankylosing spondylitis (SIR 1.14), celiac disease (1.16), Crohn disease (1.07), diabetes mellitus type 1 (1.19), discoid lupus erythematosus (1.26), glomerular nephritis chronic (1.12), Hashimoto/hypothyroidism (1.11), lupoid hepatitis (1.44), multiple sclerosis (1.11), psoriasis (1.18), Reiter disease (1.38), rheumatoid arthritis (1.07), Sjören syndrome (1.21), and ulcerative colitis (1.05).

Conclusion

Familial associations with several of autoimmune and related diseases suggest genetic sharing and challenge to gene identification.

AUTO1-0961
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

NEURONAL AUTOANTIBODIES DETECTION: EVIDENCE FOR AN EXPANDING SPECTRUM OF CLINICAL MANIFESTATIONS IN ANTI-NMDAR- POSITIVE PATIENTS.

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Background

Aim: We retrospectively analyzed neuronal surface (NSA) and neuronal intracellular/synaptic autoantibodies (NIC) results in 970 consecutive samples, from patients with autoimmune encephalitis (AE) or paraneoplastic neurological syndrome (PNS) suspicion. We correlated positive results with clinical manifestations.

Method

Material and Methods: We determined NIC by indirect immunofluorescence (IFI) on primate cerebellum and immunoblotting, and NSA by IFI on rat cerebellum, hippocampus and HEK-transfected cells with 7 neuronal surface proteins: NR1 subunit of NMDAR, AMPAR1 and R2, GABARB, LGI1, CASPR2, DPPX (CBA). Low positive results were confirmed in our laboratory, by co-localization tests, and cross-validated by immunohistochemistry (IH) in a reference laboratory.

Results

Results: We found 40 positive patients. Antigen frequencies were: NMDAR:30%, GAD:22.5%, SOX-1:10%, LGI1:7.5%, Hu:5%, CV2:5%, Yo:5%, GABARA:2.5%, SOX1+Hu:2.5%, SOX-1+GABARB:2.5 %, Hu+GABARB:2.5 %, VGCC+SOX-1:2.5 %, CASPR2:2.5 %.

Clinical manifestations of NIC-positive patients were typical as already described, while anti-NMDAR-positive patients (n=12) presented a wide spectrum of symptoms: classical encephalitis (n=4), isolated epilepsy (n=1), multiple sclerosis plus encephalitis (n=1), HIV+ patients with isolated psychosis and demyelinating syndrome plus cerebellar disease respectively (n=2). 4 additional patients were only NMDAR-positive in serum.

10 IFI-negative patients with high AE suspicion were also negative by IH. Among 5 samples with a NSA-suggestive IFI pattern on tissues, 1 was positive for GABARA by IH and CBA. An anti-CASPR2-positive result was found unspecific by IH.

Conclusion

Conclusions: IFI on brain sections and CBA, combined with immunoblotting, was a sensitive tool for diagnosis of EA and PNS. Anti-NMDAR-positive patients presented a varied spectrum of clinical manifestations.

AUTO1-0573
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

TH1, TH2 AND TH17 CYTOKINE PROFILE IN PATIENTS WITH MULTIPLE SCLEROSIS FOLLOWING TREATMENT WITH RAPAMYCIN

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Background

Management of multiple sclerosis (MS) is based on the usage of immunosuppressive and immune-modulating medications. Cytokines play an important role in the pathogenesis of MS. thus, this study aimed to evaluate the effects of rapamycin on the concentrations of Th1/Th2/Th17 serum cytokines in patients with MS

Method

Six patients with relapsing remitting MS as a case and 6 normal humans as a control group were enrolled. The patients have been received 2 mg rapamycin daily for 6 months. The humans in control group received nothing during 6 months of the experiment. Enzyme linked immunosorbent assay (Multi-Analyte ELISArray) technique was used for determination of serum concentrations of IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-17, IFNγ, TNFα, GCSF and TGF-β before and after therapy with rapamycin

Results

The mean absorbance of 10 (83.33%) out of the 12 studied cytokines showed reduction after the therapy with rapamycin including IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-17, IFNγ and TNFα. The only statistically significant reduction was observed in the absorbance of IFNγ (P=0.028). Two cytokines illustrated increase in the patients' serum after the therapy, including GCSF and TGF-β, but only increase in TGF-β was statistically significant (P=0.046). None of the studied cytokines in the control group varied significantly after 6 months

Conclusion

Rapamycin has some immunosuppressive effects, such as decreasing INFγ, which can improve the quality of life of the patients with multiple sclerosis. Also the increased level of TGF-β may also have benefits on the disease, but needs further clinical studies.

AUTO1-0404
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

INCREASED AUTOANTIBODY REACTIVITY IN SALIVA OF YOUNG ATHLETES AFTER SUBCONCUSSION

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Background

Millions of athletes in US practice sports where repetitive concussions (mild TBI) may predispose to subsequent severe neuropsychological disorders. Concussion causes Blood-brain barrier ruptures, and consequent protein leakage in CSF, blood, and also saliva. While the concussion diagnostic process is quite well assessed, less is known about subconcussive events and their effect on brain. The aim of our study was to profile the autoantibody repertoire in saliva samples of high school lacrosse and football players, to identify early diagnostic biomarkers and possible similarities between concussion and subconcussion.

Method

Counting on the Human Protein Atlas antigens resource, we applied antigen arrays to identify IgA reactivity in saliva of athletes. A discovery phase was run on 100 samples, collected pre- and post-concussion and subconcussion. Reactivity toward 1536 antigens was screened using planar arrays, and 61 targets were selected for further analysis. Beside these, 211 were added as representing proteins with biological interest in this context. A bead-based antigen array was generated, and a verification phase run on 36 samples pre and post-concussion, and 32 pre and post-subconcussion.

Results

Results show an increase in reactivity toward 16 proteins after concussion, and 14 after subconcussion. Interestingly, 3 brain-enriched proteins were in common. Increased reactivity was also identified toward proteins linked to depression.

Conclusion

This study suggests there could be a similarity between the effect of concussion and subconcussion on brain, and this could have an impact in the return-to-play decision-making. Saliva resulted suitable for autoantibody detection, and further analysis will be run to confirm our findings.

AUTO1-0445
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

PROSTAGLANDIN E2 CONTRIBUTES TO THE DEVIATION OF IMMUNE RESPONSE TO TH2/TH17 AXIS IN PATIENTS WITH NEUROMYELITIS OPTICA SPECTRUM DISORDERS

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Background

Background: Previous studies demonstrated that genetic variants in the prostaglandin pathway are associated with the risk of developing autoimmune diseases. Here, we investigated the effect of PGE2 on immune response of patients with neuromyelitis optica spectrum disorders

Method

Material and methods: 21 patients with NMOSD were studied. Cytokines and PGE_2 production following 48 hour stimulation with anti CD3 and anti CD28 was measured using a multiplexed CBA assay and ELISA assay respectively. Proliferative response of lymphocytes was measured by ^3H thymidine uptake.

Results

Results: We demonstrated that the levels of PGE2 of NMOSD patients were comparable to the healthy individuals. However, the immunoregulatory function of PGE2 in NMOSD patients was exacerbated, since proliferative response of lymphocytes stimulated by anti CD3 and anti CD28 was significantly increased in the presence of indomethacin in relation to healthy donors. The production of IL-2 and IFNɣ in the supernatant of leukocytes from treated NMOSD patients cultured in the absence of indomethacin was significantly reduced in relation to healthy control. The addition of indomethacin leads to increased production of IL-2 in patients with NMOSD confirming that PGE2 reduce Th1 cytokines.

Conclusion

Conclusions: The addition of indomethacin did not modify the levels of Th2/Th17 in NMOSD patients, which were comparable to normal individuals. Cytokines produced by both Th2 and Th17 lymphocytes contributes to the production of autoantibodies and perpetuates the inflammatory response in NMOSD.

Financial support: FAPESP, CAPES, INCT-NIM, CNPq Brazil

AUTO1-0486
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

EVALUATION AND MANAGEMENT OF AUTOIMMUNE ENCEPHALITIS IN THE PEDIATRIC PATIENTS: A CASE SERIES

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Background

Autoimmune encephalitis (AE) is emerging as a more common cause of pediatric encephalopathy than previously thought. Neurological features are movement disorders, seizures, altered conscious level, and cognitive regression. Inflammatory findings in the cerebrospinal fluid may be present but are relatively nonspecific.

Method

From January 2017 to September 2017, we diagnosed 4 patients with autoimmune encephalitis.

Results

The 4 patients included (1 boy, 3 girls; aged 10 to 17 years). Overall symptom duration before hospital admission was ≤5days. We observed all patients suffered from acute onset seizures. Only one of the patients had epilepsy history. We determine two patients had anti-N-methyl-D-aspartate receptor (NMDA) antibody while other two patients had anti TPO antibody. Magnetic resonance imaging of the brain showed some abnormalities including cortical and/or subcortical, basal ganglia, and infratentorial T2 hyperintensities with or without transient meningeal enhancement. Acyclovir was given to a patient who had HSV antibody for 21-28days. All patients received IVIG and plasmapheresis (5 to 8 days)early during the disease and three patients received pulse metyl prednisolon in addition. One patient with anti NMDA Ab had rituximab therapy. Three patients improved and discharged with some motor dysfunction from intensive care unit . They One patient was died. The patient who received rituximab therapy had better cognition and motor function than others.

Conclusion

To facilitate early diagnosis, pediatricians need to maintain a high level of suspicion when evaluating children with new-onset seizures or encephalopathy since autoimmune encephalopathies likely remain underdiagnosed.

AUTO1-0964
CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY

The incidence of ANA/ENA in patients with neuromyelitis optica positive for AQP4 autoantibodies

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Background

Neuromyelitis optica (NMO) is an autoimmune disease characterized with the presence of antibodies to aquaporin-4 (AQP4). Antinuclear antibodies (ANA) and antibodies to extractable nuclear antigens (ENA) are characteristic for systemic autoimmune rheumatic diseases (SARD). The aim of this study was to investigate the incidence of ANA / ENA autoantibodies in patients with NMO in order to investigate possible overlap of SARD with NMO.

Method

The study was conducted in a group of 24 patients positive for AQP4 autoantibodies, which are additionaly analyzed for ANA and ENA autoantibodies. Antibodies to AQP4 were determined by ELISA method (Iason, Austria). ANA antibodies were determined on HEp-2 cells with indirect immunofluorescence (IIF) method (Euroimmun, Germany). Autoantibodies to ds-DNA, histone, SS-A, SS-B, Sm, RNP, DNA topo I 1, and CENP B were determined by the AtheNA ANA-II Plus Multiplex Luminex microbead immunoassay (Zeus Scientific Inc., USA).

Results

Positive ANA IIF were found in 12 (50%) positive AQP4 patients and all of them were women. Seven of ANA positive samples (58.3%) were anti-SSA positive and 3 (25%) were anti-SSB positive while 2 (16.7%) were positive for dsDNA antibody and histone. Other tested antibodies were negative.

Conclusion

Positive ANA / ENA antibodies were found exclusively in women with positive results of antibodies to AQP4. Positive ANA antibodies were mostly related to SSA and SSB antibodies which are characteristic for Sjögren's syndrome. These preliminary results indicate the possible overlap between NMO and Sjögren's syndrome.

AUTO1-0005
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

ECONOMIC IMPACT OF CCP TEST MISCLASSIFICATION (FALSE POSITIVES) IN THE DIAGNOSIS OF RHEUMATOID ARTHRITIS IN PORTUGAL

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Background

Rheumatoid Arthritis (RA) is a chronic and progressive disease which needs to be diagnosed and treated in the early stages in order to avoid joint destruction. Anti-CCP antibodies are highly specific for RA and can help doctors to make decisions. Although the diagnostic accuracy of the CCP test used is important, the consequences of CCP misclassification have not been investigated. CCP-False Positives (FPs) patients could be managed as RA patients, bringing extra costs until correct diagnosis is made.

The aim was to simulate the economic burden of FPs for anti-CCP tests from different manufacturers, comparing the misclassification results obtained using Portuguese unit cost data.

Method

A 12-months Markov model simulated, from the hospital perspective, 1.000 RA-suspected individuals tested in secondary care with five CCP tests (EliA CCP, Quantalite CCP 3.0, Anti-CCP EDIA, Axis-Shield anti-CCP, Elecsys Anti-CCP).

Sensitivities and specificities were derived from a systematic literature review and meta-analysis.

Costs came from a published study.

Different scenarios regarding the time to achieve a correct diagnosis were considered.

Uncertainty was addressed with sensitivity analysis.

Results

Using a prevalence of 50% in the secondary care setting, FPs ranged from 1.7% (EliA CCP) to 4.3% (Elecsys anti-CCP).

Cost of FPs was lowest when using EliA(13.545€-17.157€), and highest when using Elecsys(33.863€ -42.893€).

Cost increases between 5.6 and 6.7% when the patient remains more time being considered a RA patient. Results were stable to univariate sensitivity analysis.

Conclusion

EliA CCP test demonstrates superior value from a patient, health care provider and payer perspective as a direct consequence of less false positive results.

AUTO1-1006
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

MOVING TOWARDS A MORE PRECISE DIAGNOSIS OF RHEUMATOID ARTHRITIS BY LEVERAGING ACPA FINE-SPECIFICITIES POWERED BY ARTIFICIAL INTELLIGENCE

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Background

Anti-citrullinated protein/peptide antibodies (ACPA) are important both in the pathogenesis and diagnosis of rheumatoid arthritis (RA). Several attempts to utilize ACPA fine-specificities to improve the diagnosis of RA have provided interesting insights, however, currently ACPA fine specificities are not clinically used to aid in the diagnosis of RA. This might be attributed to the lack of powerful software support which could be achieved through the application of artificial intelligence (AI).

Method

Serum from 60 RA patients and 45 controls were tested on a paramagnetic particle multi-analyte system (PMAS) for ACPA fine-specificities (n=27). Data underwent normalization by mapping to uniform distribution and applying non-linear quantile transformation. To identify peptides contributing most to variation in the data, principle component analyses (PCA) was performed taking into account sample attributes to ensure samples distributions were unbiased. Unsupervised hierarchical clustering analysis utilizing ward's linkage algorithm was subsequently performed on selected peptides to ensure samples appropriately aggregated together. Utilizing forest-based bootstrap aggregating classification, we show that our approach accurately distinguishes RA from non-RA samples.

Results

PCA using normalization approaches showed improved discrimination between RA patients and controls. Calculations considering the top 12 or the top 7 contributing peptides are shown below.

Peptides Analyzed	Sensitivity	Specificity	LR+	LR-	Odds Ratio	Total agreement	Cohen's Kappa (95% CI)
12	87.5%	92.3%	11.38	0.14	84	90.5%	0.80 (0.80- 0.80)
7	100%	86.7%	7.5	0	∞	90.5%	0.79 (0.60-0.97)

Conclusion

Our data demonstrate that the combination of ACPA testing and AI could further improve the serological diagnosis of RA.

AUTO1-0977
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

SHORT METHOD VERIFICATION OF ANTI-CITRULILINATED PEPTID ANTIBODIES (anti-CCP) ON IDS-iSYS ANALYSER

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Background

Anti-CCP are considered a diagnostic marker for rheumatoid arthritis (RA). Positivity of anti-CCP is a strong predictor of development of RA and it is associated with more destructive disease course. The aim of this study was to perform method verification for quantitative determination of anti-CCP using chemiluminiscent immunoassay (CLIA) on IDS- iSYS analyser (ZENIT RA CCP, A. Menarini diagnostics, Firenze, Italy), including comparison with electrochemiluminescence immunoassay (ECLIA) on Cobas e411 analyser (Roche Diagnostics, Mannheim, Germany) currently in use in our laboratory.

Method

Precision study was done according to CLSI EP15-A2 protocol using commercial positive control (ZENIT RA CCP Positive Control; RA +CCP) and high positive patient sample (p +CCP). Due to the assay differences (cut off <5.0 U/L for CLIA and <17.0 U/L for ECLIA), results for patient samples (N=34) were categorized as positive/negative and Cohen's kappa test was used for agreement testing (criteria: kappa >0.60).

Results

Coefficients of variation (CV) for within-run precision were 3.34% (RA +CCP) and 3.05% (p +CCP). CVs for within-laboratory precision were 4.73% (RA +CCP) and 4.55% (p +CCP). Kappa coefficient showed good agreement (κ=0.76; 95% CI 0.54-0.98) between CLIA and ECLIA.

Conclusion

Manufacturer's claim for within-run precision (4.8%) and within-laboratory precision (5.6%) were verified. IDS- iSYS anti-CCP assay showed good analytical performance and agreement to ECLIA, making it good choice for routine use in clinical laboratory.

AUTO1-0769
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

PROGNOSTIC VALUE OF ANTI-CCP ANTIBODIES IN PATIENTS WITH RHEUMATOID ARTHRITIS UNDER TREATMENT WITH DMARDS

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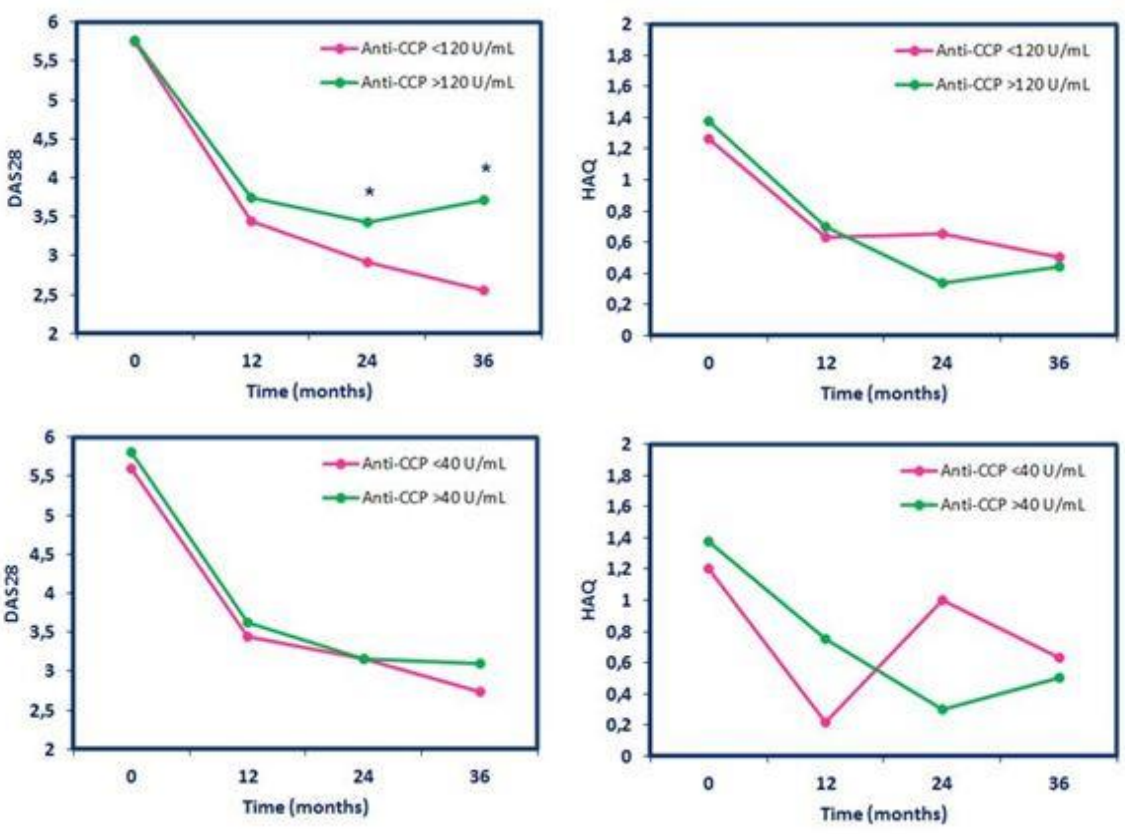
Background

Prognostic value of autoantibodies in patients with Rheumatoid Arthritis (RA) is unclear. Studies show conflicting results regarding the prognostic value of anti-CCP antibodies. The aim of our study is to study the prognostic value of anti-CCP antibodies in patients with RA.

Method

59 patients with recent diagnosed RA and median age of 53 (42-59) years were followed up during 3 years after diagnosis. The patients were treated with disease modifying antirheumatic drugs (DMARDS). Disease activity (DAS28) was assessed by CRP, ESR, 28 joint disease activity score, and the physician's global assessment of disease activity. Functional ability was evaluated by the Health Assessment Questionnaire (HAQ). Patients were stratified in two groups according the cut-offs of 40 U/mL and 120 U/mL (3xreference value).

Results The results for the monitoring of DAS28 and HAQ for the cut-offs of 40 U/mL and 120 U/mL are show in the figures



Conclusion A cut-off of 40 U/mL has not prognostic value in the patients with RA according to the evolution of DAS28 and HAQ during the three years of study. However, a cut-off of 120 U/mL allows us to stratify patients in two groups with different response to the treatment according to the DAS28 value.

AUTO1-0399
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

ENVIRONMENTAL RISK FACTORS FOR RHEUMATOID ARTHRITIS ARE CONNECTED TO THE EXPRESSION OF ANTIBODIES AGAINST SPECIFIC CITRULLINATED PEPTIDES

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Background

RA patients usually express high levels of anti-citrullinated peptide antibodies (ACPAs), and these are often present years before diagnosis. But the ACPA response consists of reactivity against numerous different antigens. Here we investigated the association between RA risk factors and immunity against specific peptides, as this may provide insight into how the pathogenic immunity in RA arises.

Method

We recruited 2249 incident RA patients from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study. We extracted exposure data for the three most validated environmental risk factors; smoking, low/no consumption of alcohol and high BMI, from an extensive questionnaire. Furthermore, the presence of 22 RA specific auto-antibodies were measured using a multiplex peptide micro array. Our statistical approach included LASSO regression to enable the detection of primary associations between exposures and antibody presence, while avoiding the detection of secondary associations due to correlation between antibodies.

Results

The presence of 15 antibodies were positively correlated with each other. Smoking was primarily associated with antibodies against citrullinated peptides of fibrinogen β-chain and hnRNP A3. Alcohol also showed primary association with antibodies against citrullinated hnRNP A3 peptides. BMI was not significantly associated with antibody presence.

Conclusion

The presence of one antibody might mediate the expression of other antibody through epitope spreading, thereby causing the observed correlation between antibodies. Our results suggested that in RA etiology, reactivity towards citrullinated peptides of fibrinogen β-chain and hnRNP A3 might partially explain the mechanism of action of smoking and alcohol.

AUTO1-0902
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

CITRULLINATION AS A TARGET FOR CD8+ T CELLS IN RHEUMATOID ARTHRITIS

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Background

The purpose of the project is to identify molecular patterns that are responsible for targeting of healthy joint tissue in patients with the autoimmune disease rheumatoid arthritis (RA). We want to investigate the T cell specificity and associated phenotype in CD8+ T cells from RA patients.

T cell recognition of self-antigens plays a major role in several autoimmune diseases, including RA. However, we have very little knowledge about the molecular patterns (antigens) that the T cells recognize with their T cell receptor (TCR). Every human harbor more than 10 million different TCRs and decoding the molecular pattern that each of these recognize has until now remained an unsolvable task. Citrullinated proteins are known to be a target for B cells in RA, and we hypothesize that citrullinated peptide might also be a target for T cells.

Method

A novel technology applying DNA barcode tags to peptide-MHC multimers has recently enabled parallel detection of 1000 TCR specificities in one sample and has brought us one step closer to solving this conundrum. We will employ this high-throughput technology on PBMC from RA patients and healthy donors to identify citrulline-specific auto-reactive T cells as well as virus-reactive T cells. We will then investigate the gene expression in these cells to gain a better understanding of the phenotypic and functional differences between auto-reactive T cells in healthy donors and in RA patients.

Results

No results yet.

Conclusion

When these mechanisms are elucidated it will become possible to specifically target the T cells responsible for tissue inflammation and destruction.

AUTO1-0391
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

STUDY OF VALUE CORRELATION BETWEEN ANTI-CCP AND RF OVER A THREE YEAR PERIOD

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Background

Anti-cyclic citrullinated peptide autoantibody (anti-CCP) and rheumatoid factor (RF) are the most useful serological markers in patients with rheumatoid arthritis.The purpose of this study is to determine the association between those two markers at patients of our Hospital (clinics and outpatient departments) during the period 07/2014-06/2017.

Method

We studied 220 patients with diagnosed rheumatoid arthritis and high levels of anti-CCP antibodies in which RF were simultaneously measured. Anti-CCP testing was done by kit ELISA anti-CCP (IgG) of EUROIMUN while the determination of RF was done by the method of chemiluminescence at the immunological analyzer ARCHITECT plus ci8200, Abbott.

Results

From 220 anti-CCP (+) patients, 169 (76,81%) were women and 51 (23,18%) were men. From women 66 (39%) presented RF values <3 IU/ml, 53 (31,3%) RF 30-200 IU/ml and 50 (29,58%) RF > 200 IU/ml . From men 15 (29,4%) presented RF values <3 IU/ml, 20 (39,21%) RF 30-200 IU/ml and 16 (31,3%) RF >200 IU/ml.

Conclusion

Positive anti-CCP were found to have a higher percentange to women than men. At RF values <30 IU/ml women overcome while at RF 30-200 IU/ml and >200 IU/ml there is a clear superiority of men.

AUTO1-0230
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

COMPARISON OF CCP2 AND CCP3 ASSAYS IN A LARGE COHORT OF ESTABLISHED RHEUMATOID ARTHRITIS (RA) AND CONTROLS

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Background

The second and third generation of CCP assays (CCP2, CCP3) are based on peptides specifically designed and optimized to detect ACPA, enhancing the immunoreactivity of the citrulline-containing epitope. The goal was to compare the performance of CCP2 and CCP3 assays.

Method

1655 samples including 968 RA patients and 687 controls (450 ankylosing spondylitis (AS) and 237 psoriatic arthritis (PsA) patients), all derived from the Swiss Clinical Quality Management in Rheumatic Diseases Foundation (SCQM) were included. ACPA were determined by CCP2 ELISA (Eurodiagnostica, Sweden), CCP3 ELISA (QUANTA Lite® CCP3 IgG) and CCP3 CIA (QUANTA Flash® CCP3 IgG) (both Inova Diagnostics, US). RF IgM was measured by ELISA (QUANTA® Lite RF IgM, Inova Diagnostics, US).

Results

The CCP2 ELISA showed a high sensitivity (71.1%) and a moderately high specificity (86.9%) with a corresponding Odds ratio (OR) of 16.3 (95% CI 12.5-21.1). The two CCP3 assays showed lower sensitivities (61.8% for the ELISA and 61.4% for the CIA), but significantly higher specificities (98.4% and 98.5% respectively), resulting in much higher predictive values, with OR of 99.3 (95%CI 54.4-181.2) and 107.5 (95%CI 57.4-201.5), respectively. When multi-parametric analyses were performed, combining ACPA and RF IgM resulted in higher OR than the individual markers and the combination of CCP3 and RF IgM resulted in a higher OR (OR= 187.0, 510/1655) than the combination of CCP2 with RF IgM (OR=36.7, 565/1655).

Conclusion

CCP3 showed a better overall performance than CCP2 in this cohort of RA and controls, when analyzed individually as well as in combination with RF IgM.

AUTO1-0672
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

RETROSPECTIVE STUDY OF ANTI-CCP DETECTION BY THE FULLY AUTOMATED COBAS° (ROCHE) SYSTEM ON 1582 RHEUMATOLOGY PATIENTS: ASSESSMENT OF CUT-OFF VALUES FOR HIGH DIAGNOSTIC SPECIFICITIES.

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Background

Anti-citrullinated protein/peptide antibodies (ACPAs) are the most specific serological markers for rheumatoid arthritis (RA). From 2010 they belong to the ACR/EULAR classification criteria for the disease. Many sensitive anti-CCP (cyclic citrullinated peptide) tests for their detection were developed in multiparametric fully automated systems. However, these tests have not always benefited from careful assessment of their diagnostic specificity.

Method

In daily practice at the University-Hospital of Toulouse, ACPA are measured by two methods: detection of anti-citrullinated human fibrinogen autoantibodies (AhFibA) by a home-made ELISA, and anti-CCP by immunocapture with the Cobas°(Roche) automated system. From 2014 to 2016, 2701 patients from the Rheumatology Center had ACPA detection. Final diagnoses were extracted from medical reports for 1582 patients: 672 (42.5%) had RA and 910 (57.5%) had non-RA rheumatologic diseases. We determined the optimal cut-off values for anti-CCP in those patients.

Results

At the manufacturer threshold (17 U/mL), anti-CCP diagnostic sensitivity was 76.6 % and diagnostic specificity only 93.5%. To reach specificities of 95% and 98.5%, the thresholds had to be raised to 22.5 and 140 U/ml, the related sensitivities being 76.3% and 61.2%, respectively. At the previously determined 95% and 98.5% specificity thresholds, the diagnostic specificities of the AhFibA assay, were 97.3% and 97.7% respectively. The related thresholds for anti-CCP were 51 and 63 U/mL.

Conclusion

In real-life conditions of a University-Hospital, the cut-off values of the automated anti-CCP Cobas (Roche) test must be put up to 50 U/ml to get a 97.3% diagnostic specificity and, better, to 140 U/mL, to obtain a specificity of 98.5%.

AUTO1-0587
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

CD40 AND CD40L EXPRESSION IN RHEUMATOID ARTHRITIS: ASSOCIATION WITH CLINICAL ACTIVITY AND AUTOANTIBODY PRODUCTION

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Background

The CD40/CD40L costimulatory pathway is involved in cellular and humoral immune responses development. In rheumatoid arthritis (RA), CD40/CD40L is pathogenic stimulating autoantibody production and expression of proinflammatory mediators. This study aimed to evaluate CD40 and CD40L expression and its association with clinical activity and autoantibody levels in RA.

Method

Thirty-eight RA patients and 10 control subjects (CS) matched by age and gender were included. Relative mRNA expression of *CD40* and *CD40LG* was determined by real-time qPCR in total peripheral leucocytes. Soluble levels of CD40 and CD40L were quantified by ELISA and membrane protein expression was determined in peripheral blood T cells, B cells and monocytes by flow cytometry.

Results

RA patients had higher frequency of CD4+CD40+ T cells, CD4+CD40L+ T cells and CD40L+ B cells compared with CS. No differences regarding CD40 and CD40L monocyte expression between RA patients and CS were observed. A tendency towards greater expression of CD40L (mRNA, soluble and membrane protein) according to clinical activity was noted in RA patients. However, CD40L expression was not associated with RA clinical parameters. There were no significant differences regarding *CD40* mRNA expression and soluble CD40 between RA patients and CS. Levels of soluble CD40 along with the expression of CD40 and CD40L in B cells and CD40 expression in monocytes were inversely correlated with anti-CCP.

Conclusion

Results support previous evidence regarding CD40L expression as a clinical activity marker in RA. A negative association between CD40 expression levels and autoantibody production was identified for the first time, more studies are needed addressing this.

AUTO1-0931
CITRULLINATION AND AUTOIMMUNITY: ANTI-CCP

ANTI–CARBAMYLATED PROTEIN ANTIBODIES ARE PRESENT IN FIRST-DEGREE RELATIVES OF RHEUMATOID ARTHRITIS INDIVIDUALS AND THEY ARE ASSOCIATED WITH CLINICAL MANIFESTATIONS OF ARTHRITIS

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Background

Association studies in rheumatoid arthritis (RA) have been focused in asymptomatic individuals with higher risk to RA such as first-degree relatives (FDR). New autoantibodies against carbamylated proteins(anti-Carp) have been discovered and associated with radiological progression. We analyzed whether anti-CarP are already present in healthy individuals(HI) and FDR and how the anti-CarP antibodies relates to other autoantibodies clinical symptoms and obesity.

Method

118 FDR and 118(HI) matched by age and gender were included. A strict medical history related to RA was obtained. Anti-Carp-fetal calf serum protein, IgM-RF, ACPAs, leptin, CRP and ESR were evaluated. An association analysis was made to evaluate the relationship between anti-Carp levels and rheumatologic conditions.

Results

In FDR, 22.2% were current smoker, leptin high in 26.27%, 16.9% APCA, 4.23% IgM-RF and 26.3% Anti-Carp were positive, 19.5% were autoantibody single-positive, 6.78 % double–positive and is no one triple positive.In controls, leptin high in 12.7%(p=0.004), RF in 2.5%(p=0.71), ACPA 6.8%(p=0.013) and anti-Carp 15.3%(p=0.027) were positive. In positive individuals Anti-Carp, 16.3% had CRP>3mg/L(p = 0.030), 12.2% had >1 swollen joint(p= 0.053), 8.8% had >1 painful joint of which 38.8% and 78.9% were FDR respectively. Anti-Carp was associated with >1 swollen joint adjusted to the presence of leptin (OR=4.08, CI 95% 1.22-13.56,p=0.022) in FDR.

Conclusion

Anti-Carp in FDR were similar with previous reports from patients who fulfilled criteria for RA obtained before its diagnosis. A high frequency of anti-Carp in FDR compared to HI. The presence of anti-CarP antibodies may have clinical value in the FDR.

AUTO1-0551
COMPLEMENT IN AUTOIMMUNITY

Complement Factor H is increased and associated with elevated oxidative stress markers and pro-inflammatory cytokine IL-1 β in Algerian Behçet's disease Patients

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Background

Behçet's disease (BD) is a multisystem disease. It stands at the crossroad between autoimmunity and auto-inflammatory disorders. In the present study, we aimed to assess the plasma level of complement factor H (CFH) and elucidate its possible correlation with oxidative stress markers and proinflammatory cytokine IL-1β in Algerian BD patients.

Method

We investigated the CFH, stress oxidative markers (Nitric oxide (NO), Advanced oxidized proteins products (AOPP)) and IL-1β in Algerian BD patients (n=78) : Active BD patients (ABP, n=28) and Inactive BD patients (IBP, n=50) referring to disease activity and clinical manifestations compared to healthy controls (HC, n=41). Mann–Whitney U and Spearman tests were used for statistical analyses.

Results

CFH levels significantly increased in ABP and IBP ($p<0.0001$) compared to HC, whereas there is no significant difference ($p=0.05$) between ABP and IBP. NO and AOPP levels significantly increased in ABP ($p<0.001$) compared to IBP and HC and in IBP ($p<0.001$) versus HC. ABP displayed higher plasma levels of IL-1β ($p<0.05$) versus IBP and HC ($P<0.001$). In addition, IBP showed higher levels of IL-1β ($p< 0.01$) versus HC.

CFH significantly and positively correlated with AOPP in BD patients and ABP ($r=0.414$, $p=0.0015$ and $r=0.5858$, $p=0.0139$ respectively). Moreover, CFH positively correlated with NO ($r=0.290$, $p=0.028$) and with IL-1β ($r=0.523$, $p<0.05$) in BD patients.

Conclusion

Our study highlights an overexpression of CFH correlated with high levels of oxidative stress markers and IL-1β. We suggest to further study this relationship to illuminate alternative paths of therapeutics in BD.

AUTO1-1005
COMPLEMENT IN AUTOIMMUNITY

PEMPHIGUS FOLIACEUS AND COMPLEMENT SYSTEM HAPLOTYPES

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Background

Pemphigus foliaceous (PF) is the only autoimmune disease to be endemic. In Brazil, it is also called *fogo selvagem* (wild fire), due to painful skin blisters left by the loss of epidermal cell adhesion (acantholysis). PF patients present specific autoantibodies against epitopes of desmoglein 1, a desmosomal protein. Skin blisters of PF contain several components of the complement system (CS) that is one of the main mechanisms against infection and of antibody-mediated immunity, whose genetic polymorphisms may alter the efficiency of cascade activation and regulation.

Method

We extracted genotyping results of 992 SNPs of 44 CS genes from genome-wide genotype data (CoreExome-24 v1.1 Illumina®) of 230 patients and 194 controls. After excluding SNPs with minor allele frequency less than 1% and out of Hardy-Weinberg equilibrium in controls, we reconstructed 20 haplotypes from 236 SNPs, of which 4 were associated with PF.

Results

One belongs to the *MASP1* gene that encodes a serine protease from the lectin CS pathway, also able to initiate the MAPKp38 signaling cascade involved in acantholysis (OR=1.63, p=0.021). Another occurred in *C9*, whose product is part of the destructive membrane attack complex found deposited in lesional PF skin but not in healthy skin: *C9* (OR=1.57, p=0.028). The two other haplotypes belong to genes encoding receptors for complement components, as *ITGAX* for the iC3b opsonin (OR=0.56, p=0.005) and *CR1* for C3 fragments (OR=1.62, p=0.018).

Conclusion

The associated haplotypes confirmed the importance of the CS in PF and revealed possible new therapeutic targets in the disease.

AUTO1-1029
COMPLEMENT IN AUTOIMMUNITY

PEMPHIGUS FOLIACEUS AND GENETIC POLYMORPHISMS IN LECTIN PATHWAY GENES

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Background

Pemphigus foliaceus (PF) is an autoimmune endemic disease, causing painful skin blisters. The lectin pathway of complement is initiated by the recognition of exposed sugar and acetylated residues by ficolins (FCNs) and collectins (MBL) associated with serine proteases (MASPs). FCN-2 and MBL were formerly found deposited on the basal membrane epithelial zone of patients with pemphigus vulgaris.

Method

We genotyped 30 SNPs in the FCN1, FCN2, FCN3, MBL2, MASP1 and MASP2 genes in up to 300 PF patients and 300 controls, using multiplex PCR-SSP and microarray hybridization, using logistic regression.

Results

Individuals carrying the regulatory FCN1_rs2989727*A allele and the intronic FCN3 haplotype rs28362807*ins_rs4494157*A were more resistant against PF (OR=0.54, p=0.016 and OR=0.55, p=0.018, respectively). In contrast, homozygotes for FCN3_ rs28362807*del_rs4494157*C were more susceptible (OR=1.96, p=0.006), as well as individuals carrying the MBL2 haplotype HYPA (OR=2.66, p=0.036), associated with very high MBL levels. The MASP2*TDVRC haplotype and GA/GA (rs2273344*G and rs9430347*A) genotype, both associated with the highest MASP-2 levels, also increased susceptibility to the disease (OR=4.97, p= 0.02 and OR=1.56, p=0.001, respectively). Finally, three MASP1 haplotypes increased resistance against the disease (OR=0.1-0.3, p=0.001), whereas one increased susceptibility (OR=4.6, p<0.001).

Conclusion

The associations highlight the relevance of the lectin pathway activation in PF and point to possible new therapeutic targets in the disease.

AUTO1-0782
COMPLEMENT IN AUTOIMMUNITY

CLINICAL SIGNIFICANCE OF ANTI-C1Q AUTOANTIBODIES AS A BIOLOGICAL MARKER OF LUPUS NEPHRITIS IN A PEDIATRIC POPULATION

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Background

A considerable number of Systemic Lupus Erythematosus (SLE) patients present Lupus Nephritis (LN), often characterized by flares that can lead to chronic renal failure. Early biological markers may identify patients at high risk of developing such flares, which are known to be clinically difficult to predict. The aim of this study was to determinate the values of circulating anti-C1q autoantibodies (AC1q) alone or in combination with other markers, for accessing LN in patients with SLE.

Method

A retrospective analysis was carried out on a group of 75 pediatric patients from Centro Materno-Infantil do Norte, in which AC1q were requested during screening and follow up of SLE.

Results

The diagnosis of SLE was established in 38 patients, of whom 14 presented active LN with AC1q and anti-double stranded DNA autoantibodies (anti-dsDNA) increased in 100% and 86% of the cases, respectively. The Sensitivity, Specificity, Positive and Negative Predictive Values (PPV, NPV) of AC1q and anti-dsDNA are described in Table I. A combination of AC1q with anti-dsDNA exhibited a similar Specificity and Sensitivity for identification of patients with active SLE and LN relative to AC1q alone. The absence of both autoantibodies was associated with the highest NPV (91,6%).

	AC1q	Anti-dsDNA	AC1q + Anti-dsDNA
Sensitivity	83,1%	84,8%	84,8%
Specificity	81,6%	73,7%	81,1%
PPV	74,3%	66,7%	62,7%
NPV	89,4%	88,6%	91,6%

Conclusion

Our results confirm that AC1q were increased in all SLE patients with active renal involvement, suggesting that it may be a reliable biological marker. The absence of AC1q and anti-dsDNA was associated with a very low risk of renal flare, thus their simultaneous detection is of interest for the follow-up in SLE patients with renal involvement.

AUTO1-0772
COMPLEMENT IN AUTOIMMUNITY

BETA STRUCTURAL ANTIMICROBIAL PEPTIDES AS REGULATORS OF COMPLEMENT

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Background

It is well known that complement is involved in the pathogenesis of many autoimmune diseases such as SLE, rheumatoid arthritis, autoimmune hemolytic anaemia and other. Thus complement regulators might be useful for prevention or treatment of these diseases. Antimicrobial peptides (AMPs) in addition to their antimicrobial activity have a wide range of immunomodulatory properties. It is known that defensins and some other β-sheeted AMPs can interact with complement protein C1q and influence on the level of complement activation.

Method

We investigated the interaction of some AMPs which form an antiparallel β-sheet (defensins, protegrin, arenicin, tachyplesin) with C1q and their influence on complement activation. Intermolecular complexes between AMPs and C1q were revealed by peroxidase labeled C1q or by anti-C1q antibodies as well as by SPR. To evaluate the influence of AMPs on complement activation we utilized sheep red blood cells as a target of complement. The activation of complement in human serum was assessed by cell lysis in photometric assay.

Results

We revealed that peptides studied form protein-protein complexes with C1q. In agreement with literature data, we observed decreased activation of complement in presence of defensins HNP-1-3 and increased activation in presence of tachyplesin-1. Arenicin-1, a peptide homologous to tachyplesin, and protegrin-1 also stimulate complement activation at low doses. However, we found that at high concentrations tachuplesin-1, arenicin-1 and protegrin-1 display reverse effect and act as complement inhibitors in hemolysis assay.

Conclusion

These data suggest that β-structural AMPs can be useful tool for directional regulation of complement possibly suitable for autoimmune diseases correction.

AUTO1-0126
COMPLEMENT IN AUTOIMMUNITY

HYPOXIA PROMOTES THE PATHOGENESIS OF RA VIA MICRORNA-X ENHANCING C5A-ASSOCIATED INFLAMMATION

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Background

Hypoxia and C5a are pivotal drivers of rheumatoid arthritis (RA). However, the relationships between them and how they work in driving the progression of RA are less clearance.

Method

FACS, realtime-PCR, and WB assays and in vivo measurements in mice of experimental collogen-induced arthritis were performed in the research.

Results

Here we show that hypoxia promotes C5a-mediated inflammatory responses of monocyte-dervied dendritic cells (MoDCs) via upregulating C5aR1, characterized by release of large amount of inflammatory cytokines and induction of Th17 generation. Interestingly, the upregulation of the C5aR1 expression by hypoxia is dependent on two microRNAs (miR), miR-x and miR-y (named temporarily due to unpublished) which both are increased in MoDCs by hypoxia and reported to be deregulated in RA. The abundance of miR-x is far more than miR-y, so, a mouse model deficient in miR-x has been established. As expected, miR-$x^{-/-}$ mice are resistant to collagen-induced RA (CIA), and transferring miR-$x^{-/-}$DCs overexpressing C5aR1 by recombinant adenovirus carrying the *C5aR1* gene can rescue the sensitivity of miR-$x^{-/-}$ mice to CIA.

Conclusion

So, we conclude that hypoxia promotes the pathogenesis of RA via miR-x enhancing C5a-associated inflammation.

AUTO1-0063
COMPLEMENT IN AUTOIMMUNITY

The Purpose of Temperature of Fever

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Background

unfortunately none of medical books describes the purpose of temperature of fever.**Method**

When the disease becomes threat to life or organs blood circulation decreases, Temperature of fever will emerges to increase prevailing blood circulation. And it acts as a protective covering of the body to sustain life.

When blood flow decrease to brain, the patient becomes fainted-delirious .If we try to decreases temperature of fever, the blood circulation will further reduced. Blood circulation never increases without temperature increase. Delirious can never be cured without increase in blood circulation.

We can answer almost all the questions about fever with this definition -Magic answer. If avoid or evade from this definition we will never get proper answer to even a single question.

Results

Experience gained by me for more than 29 years treating persons with fever in reduction of fever temperature.
Two ways to increase blood circulation. 1. Never allow body temperature to lose to the atmosphere. 2. Apply heat from outside to the body. When the temperature produced by body due to fever and heat which we applied on the body combines together, the blood circulation increases.

Then body will stop to produce heat to increase blood circulation. And body will get extra heat from outside without any usage of energy.

Conclusion

The actual treatment to fever is to increase blood circulation. The temperature of fever is not a surplus temperature or it is not to be eliminated from the body. During fever, our body temperature increases like a brooding hen`s increased body temperature.

AUTO1-0460
COMPLEMENT IN AUTOIMMUNITY

MORNING/EVENING FLUCTUATION OF COMPONENTS OF THE COMPLEMENT SYSTEM: RESULTS FROM A PILOT STUDY

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Background

Some authors found nadir serum levels of C4 and C3 levels, along with C3a at night time, with others finding insomnia when pro-inflammatory components exhibit increased serum levels. We here report morning and evening day-time serum levels of CH50, C4, C3, cortisol, PTH and 25-hydroxy-vitamin D at 07 :00 AM and at 07 :00 PM, motivated none the least for assurance of good pre-analytical laboratory practice when exploring complement.

Method

12 healthy adult men and 8 women voluntary participants agreed for a fasting venipuncture in the morning and having normally eaten through the day in the evening. C4 and C3 serum levels were measured on a Cobas (Roche Diagnostics, Switzerland) modular analyzer, CH50 was estimated using the COMPL300 ELISA of Wieslab (Malmö, Sweden). CRP, 25(OH)vitamin D, PTH and Cortisol concentrations were assessed with ECLIA on the Roche Cobas 6000 platform

Results

With the exception of higher PTH levels in the evening (3.12 – 5.46, 95% CI) compared to the morning (2.93 – 4.65, 95% CI), means and medians values of all analytes fell within the established reference intervals. Cortisol levels were measured as an internal positive control for diurnal fluctuations (morning: 294-522 nmol/l, 95%CI evening:106-136 nmol/L, 95%CI).

Conclusion

The concentrations of complement components C4 and C3 assessed as well as CH50 surrogate assay did not yield significantly different values between early morning and evening. This does not exclude their participation in the circadian metabolome but at least, patients with autoimmune disease can give their blood sample independently from daytime and from eating habits.

AUTO1-0311
COMPLEMENT IN AUTOIMMUNITY

INCREASED HYDROPHOBICITY IN THE GLOBULAR HEADS OF HUMAN C1q CORRELATES WITH THE DEGREE OF ITS AUTOANTIGENICITY

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Background

Human C1q is the recognition molecule of the classical complement pathway. In addition to its physiological activity in the complement system, C1q is also implemented in pathological conditions, mostly autoimmune disorders, in which C1q appears to expose autoepitopes targeted by anti-C1q autoantibodies. The exposure of these epitopes is known to be associated with conformational transitions due to immobilisation of C1q.

Method

In our study we designed a model system using the amphiphilic polyzwitterion (PZ), poly(ethylene oxide-b-N,N-dimethyl(methacryloyloxyethyl) ammonium propanesulfonate) as a tool to induce conformational transitions in C1q during its immobilization. We analysed the influence of PZ during immobilization of the native C1q and the recombinant analogues of the globular fragments of its three chains, designated ghA, ghB and ghC on their subsequent recognition by anti-C1q autoantibodies, present in the sera of patients with Lupus Nephritis (LN) by ELISA. The effects of the interactions of PZ with C1q and its globular domains were monitored by fluorescence spectroscopy.

Results

We found that both analysed concentrations of PZ, 25 mM and 50 mM, were applicable for inducing conformational transitions which resulted in increased recognition of C1q and ghB by the LN autoantibodies. Analysing the fluorescence data for the interactions of C1q and its globular heads with PZ we registered conformational changes within the protein structure.

Conclusion

In summary, the registered conformational transitions displayed a hydrophobic enhancement of the protein microenvironment due to the presence of hydrophobic binding sites in ghB which consequently affected the autoantigenicity of the whole C1q molecule.

AUTO1-0127
COMPLEMENT IN AUTOIMMUNITY

TLR7/9-triggered CD59 downregulation of plasmacytoid dendritic cells via microRNA-let-7b/i contribute to the complement-mediated protection in systemic lupus erythematosus

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Background

Plasmacytoid dendritic cells (pDCs) are outstanding in producing interferon-a (IFN-a) in response to exogenous or endogenous TLR7/9 activators such as single-stranded RNA, unmethylated CpG-ODN and anti-self-nucleic acid immune complexes (ICs). Activated pDC and type I IFN drive lupus pathogenesis. However, what mechanisms regulate the survival of activated pDCs has not been fully characterized. Complement-mediated cytotoxicity (CMC) is generally not a severe threat to oneself because of the protection by complement regulatory proteins highly expressed on most mammalian cells.

Method

We collected the sera and PBMCs from SLE patients and healthy donors for analysis and culture. Assays of flow cytometry, confocal microscopy, western blot and qPCR were also performed in this research.

Results

We showed that complement regulatory protein CD59 expression on pDCs of the SLE patients was decreased significantly compared with that of healthy population, and pDCs in active-phase SLE were more sensitive to CMC than healthy pDCs because of losing the protection by CD59. Furthermore, we found that miR-let-7b/i targeted to inhibit the expression of CD59, and its expression was upregulated in pDCs by TLR7/9 pathways which could be inhibited by p38 inhibitor, confirming that the CD59 expression during pDC activation was regulated via TLR7,9/P38/miR-let-7b/i axis.

Conclusion

Considering that complement reduction is one of clinical features in SLE due to excessive consumption, we speculated that CMC to pDCs was impaired, and as a result led to the accumulation of activated pDCs, promoting the pathogenesis of SLE. So, our findings outline a novel mechanistic explanation for its protective role by complement in SLE.

AUTO1-1033
COMPLEMENT IN AUTOIMMUNITY

RELATION OF OXIDATIVE STRESS PARAMETERS AND INFLAMMATORY MARKERS IN RA AND PSA PATIENTS

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Background

It is considered that oxidative stress, which cause disruption of the oxidative-antioxidant balance, is one of the factors playing a crucial role in the pathogenesis of rheumatic diseases with autoimmune background, such as RA and PsA. The aim of the study was to verify the relationship between oxidative-antioxidant balance parameters and C-reactive protein (CRP), White Blood Cells (WBC), Erythrocyte sedimentation rate (ESR).

Method

The study group consisted of 28 PsA patients (42±12 age), 32 RA patients (48±16 age) and 15 healthy subjects (44±11 age). In the blood samples were determined ESR, WBC and CRP with routine laboratory methods. The total antioxidant status (TAS) was determined with the commercial kit (Randox, UK), total oxidant status (TOS) was determined based on the method developed by Erel.

Results

There was a positive correlation between TOS and CRP in patients with PsA (p=0,007) and RA (p=0,006), and TOS and ESR in RA (p=0,010). There was also a negative correlation between TAS and ESR (p=0,025), TAS and WBC (p=0,010) in patients with PsA. In patients with RA, a negative correlation was found between TAS and CRP (p=0,017).

Conclusion

The total oxidative status significantly increases with inflammation as assessed by CRP in RA and PsA patients. However, the negative correlation of TAS and inflammatory markers demonstrates the compensatory ability of the organism to improve the total antioxidant status of RA and PsA patients. The lack of such a correlation in the control group may also suggest a positive effect of disease-modifying drugs on the oxidative-antioxidant balance.

AUTO1-0793
COMPLEMENT IN AUTOIMMUNITY

Serum Complement Factor I is Associated with Disease Activity of Systemic Lupus Erythematosus

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Background

Although aberrant complement activation is involved in the pathogenesis of systemic lupus erythematosus (SLE), the role of complement regulatory proteins in disease activity of SLE remains limited.

Method

We enrolled the pediatric-onset SLE patients from our cohort study over 10 years. The clinical and laboratory data including SLEDAI disease activity score, and serum complement factor H (CFH), CFI, CD46, C5a, and C5b-9 in the active and remission phases were determined. Glomerular C5b-9 deposition as a complement activity marker was also examined.

Results

Forty patients (35 female and 5 male, aged 13.9 ± 3.8 years) met the criteria of investigation were assessed. Fever and kidney were the most common symptom and organ involved, respectively. Mean SLEDAI in the active and remission phases were 12.6 *vs* 1.7, respectively. All patients exhibited lower serum C3, C4, CFH and CFI and higher serum anti-dsDNA and CD46 in the active phase. There was a significant difference in serum CFH, CFI and CD46 between active and remissive phases. Serum CFI but not CFH and CD46 level was negatively correlated with SLEDAI score in active phase. Compared to classical activity markers, serum CFI was superior to C4 and anti-dsDNA in reflecting disease activity and also significantly correlated with white blood count and hemoglobin. Glomerular C5b-9 depositions were detected in patients with nephritis during active phase but not in disease controls.

Conclusion

Serum CFI level may not only be a promising biomarker for disease activity of SLE, but also reflects the hematological features of SLE.

AUTO1-0204
COMPLEMENT IN AUTOIMMUNITY

TOTAL COMPLEMENT ACTIVITY (CH50): EVALUATION OF THERMOSTABILITY AND COMPARISON OF 2 LIPOSOME BASED ASSAYS

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Background

Total complement activity (CH50) is considered thermolabile, requiring the preservation of serum samples at -80°C prior to analysis. The reference complement mediated hemolysis of antibody sensitized erythrocytes is being replaced by liposome-based assays for practical and standardization reasons.

Method

We studied time dependent degradation at 4 and 20°C and evaluated the Optilite®CH50 kit on the Optilite turbidimeter (The BindingSite, Birmingham, UK) versus the AutokitCH50 (Wako, Neuss, Germany) on P-modular (Roche, Rotkreuz, Switzerland). Analytical performance of Optilite®CH50 was inferred from duplicate between-run measurements (CLSI EP5-A2) on 2 levels of commercial control material.

Results

CH50 was relatively stable at 4°C for 24 hours; the activity decreased with 5% after 6 hours and with 10% after 24 hours. At 20°C, 10% degradation was seen at 6 hours and 23% after 24 hours. Comparing 33 patient samples (22.26 to 87.30 U/mL) resulted in a Spearman correlation coefficient of 0.942. Passing-Bablok regression (y = 1.21 [95%CI: 1.01–1.45] x + -14.6 [95%CI: -26.1– -5.84]) revealed a significant positive proportional and negative systematic bias versus AutokitCH50. The Optilite®CH50 met the predetermined criteria for total imprecision (<8.3%), bias (<6.7%) and total error (<20%). Clinical interpretation corresponded in 15/40 patients; 16/40 patients had a normal activity with AutokitCH50 assay and a decreased activity with Optilite®CH50, applying current manufacturer's reference ranges (Autokit: 31.6 – 57.6 U/mL, Optilite: 41.68 – 95.06 U/mL).

Conclusion

CH50 degraded 10% after 24 hours at 4°C.Performance of Optilite®CH50 meets our predetermined criteria. Ungoing verification of reference ranges towards lower levels will result in a better concordance with AutokitCH50.

AUTO1-0117
COMPLEMENT IN AUTOIMMUNITY

COMPLEMENT REGULATORY PROTEIN CD59a ASSOCIATED WITH IMMUNE LIVER DAMAGE IN TRICHLOROETHYLENE-SENSITIZED BALB/c MICE

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Background

Complement system, a complex innate immune surveillance system, plays a key role in the pathogenesis of tissue damage. Complement was activated and tightly regulated by complement regulatory protein (CRP) to maintain the balance between efficient destruction and unwanted injury in the tissue. CD59 is a membrane-bound CRP and can reduce the formation of the membrane attack complex (MAC) via restricting complement excess activation. Trichloroethylene (TCE), a major occupational and environmental contaminant, can cause multi-organ damage characterized by dysregulation of the complement activation in human and experiment animals. But the roles of CD59 in liver damage induced TCE sensitization has not been examined.

Method

We evaluated the changes of CD59a (one isoform of CD59, the key regulator of the terminal complement pathway) expression in liver tissue and investigated the relationship between CD59a expression and MAC formation, NF-kB activation detected by p-IkBα and nuclear p65, liver damages in a BALB/c mouse model of TCE skin sensitization with or without soluble recombinant rat CD59-Cys (sCD59-Cys) pretreatment.

Results

CD59a expression was decreasing in the liver of TCE-sensitized positive mice vs. TCE-sensitized negative and control mice, along with an increase in MAC deposition, upregulation of inflammatory cytokine and liver damage. sCD59-Cys were alleviated liver injury and suppressed by inflammatory cytokine, with reductions in MAC deposition and a concomitant inhibition of NF-kB activation.

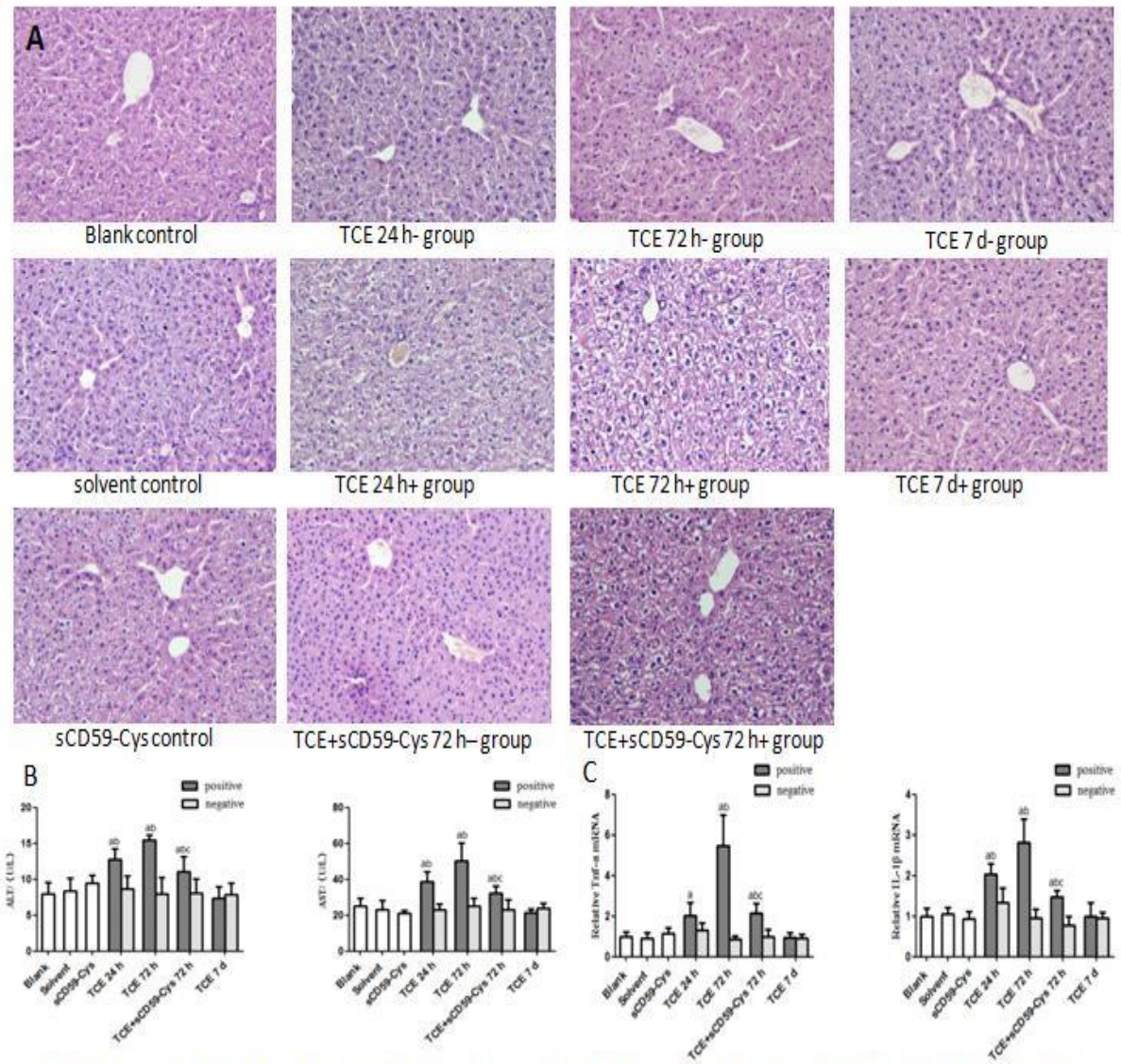

Fig. 1 Liver damage caused by TCE sensitization and sCD59-Cys pretreatment. (A) H&E staining of liver(scale bars, 400μm). (B) Serum ALT and AST tests. (C) qRT-PCR analysis of TNF-α and IL-1β mRNA in liver.

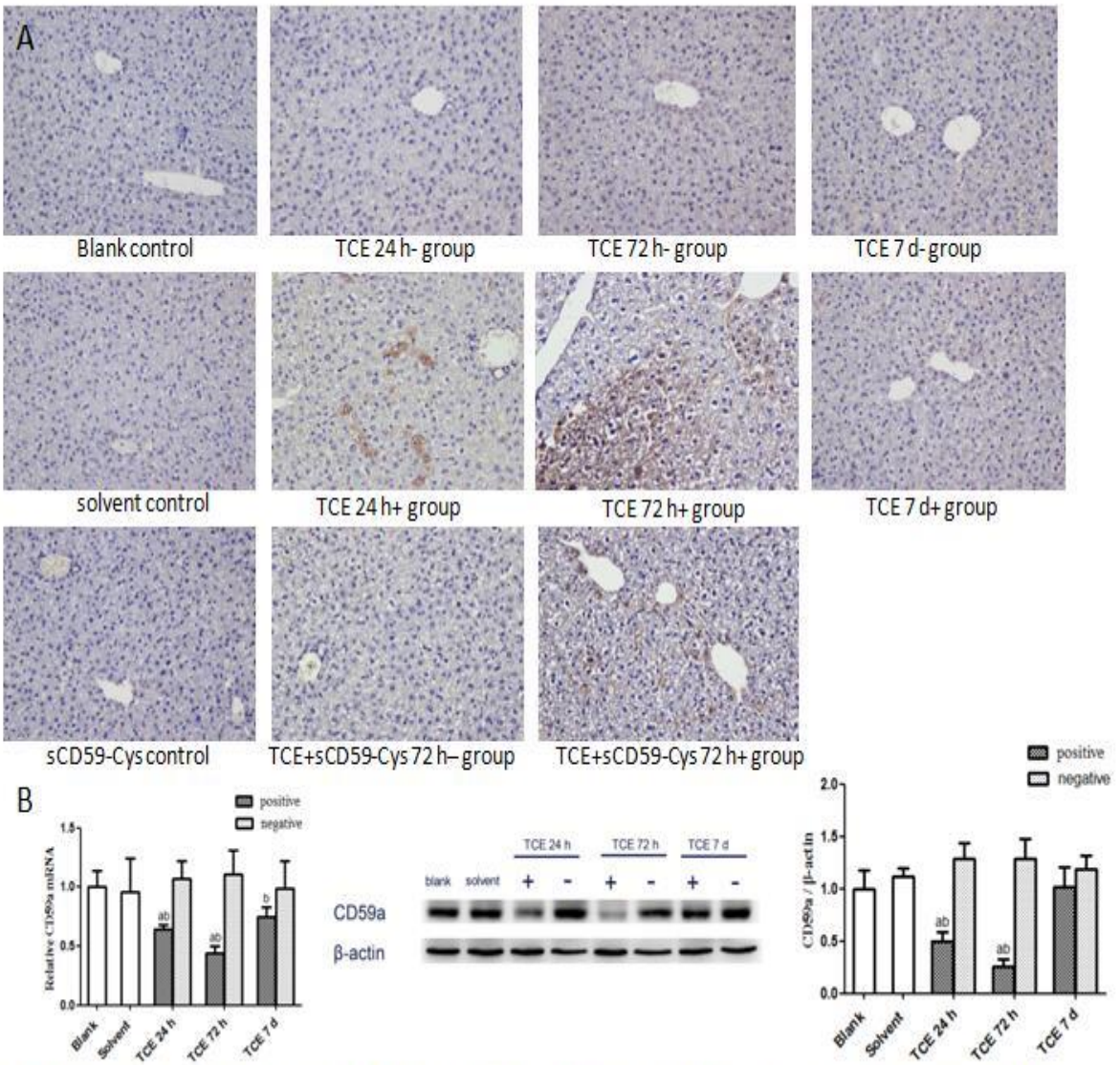

Fig. 2 MAC deposition and expression of CD59a in the liver. (A) Representative immunohistiochemistry images of MAC deposition in liver(scale bars, 400μm).(B) qRE-PCR analysis of CD59a mRNA and western blot measure of CD59a in the liver.

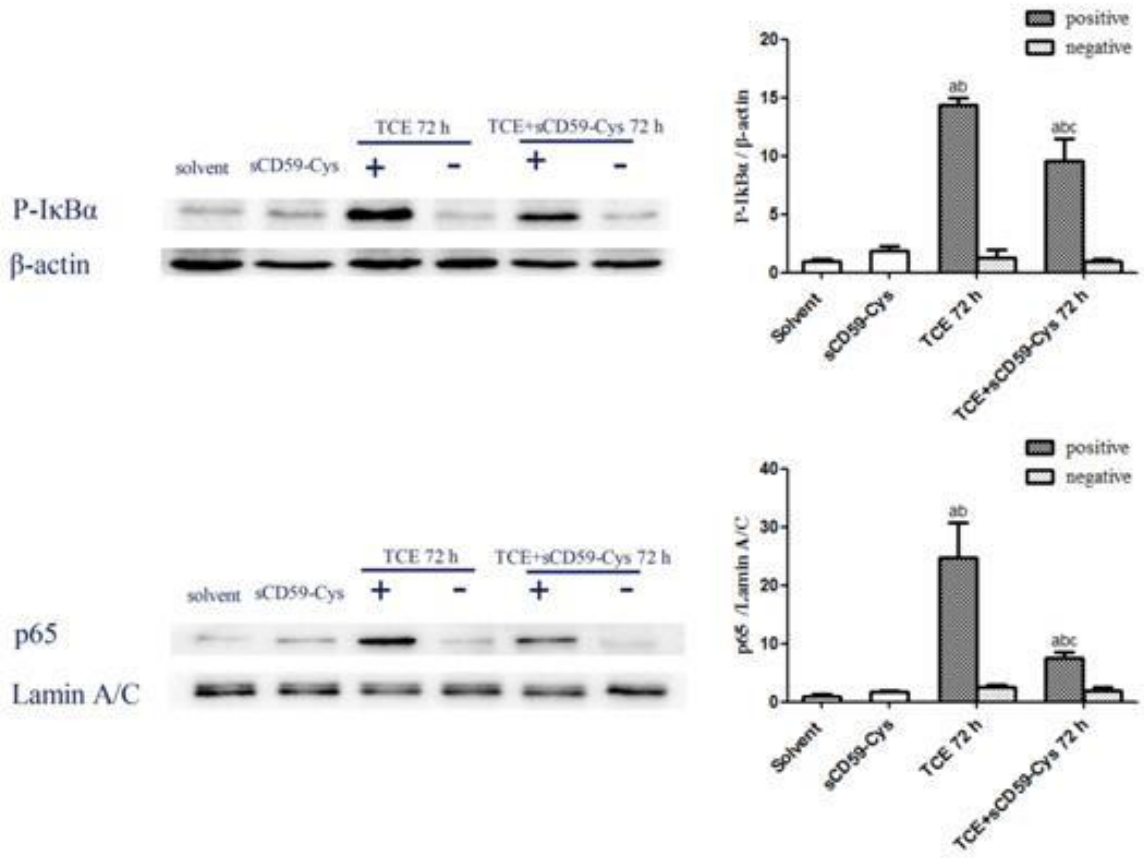

Fig.3.sCD59-Cys suppressed NF-κB activation by western bolt measure of phosphorylated IκBα and nuclear NF-κB p65 in the liver of TCE-sensitized mice.

Conclusion

These results demonstrate that CD59a is an important regulator of MAC-mediated liver damage through activating NF-kB pathway in TCE-sensitized mice. Therefore, CRP may provide a novel option for preventing harm from environmental TCE exposure.

AUTO1-0134
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND CRP/ACPA POSITIVITY IN ALGERIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Vitamin D (VD) displays immunomodulatory activities and has been proposed as a potential player in the pathogenesis of rheumatoid arthritis (RA).

Objective. The aim of this study was to estimate the prevalence of vitamin D deficiency in patients with rheumatoid arthritis as compared to healthy controls and to analyze the association between levels of vitamin D and CRP(C-reactive protein) /ACPA (anti citrullinated protein antibody) positivities.

Method

This is a retrospective study on data obtained from 115 patients fulfilling ACR 1987 criteria for RA and 104 healthy controls. All participants were not receiving VD supplements.

Serum vitamin D levels were measured using the chemiluminescent immunoassay method (CLIA)

Levels of VD at 30 and 10 ng/ml were the cut-off values for VD insufficiency and deficiency respectively.

CRP (mg/dl) was measured by the nephelometric method and ACPA antibodies were evaluated using enzymatic linked immuno-assay (ELISA).

Results

The mean value of VD was lower in healthy controls (15 ng/ml) compared to patients with RA (25 ng/ml).

60% of our patients were insufficient in VD, while 10% had a VD deficiency.

Our study showed a correlation between low VD values and positive CRP compared to patients with negative CRP (23 ng/ml vs 29ng/ml; P=0,023). Moreover, a statistically significant association was also found between low VD levels and ACPA positivity (23ng/ml vs 28ng/ml; P=0, 03)**Conclusion**

The results of this analysis indicated that vitamin D deficiency is quite common in Algerian patients with RA.

CRP and ACPA values are inversely related to 25(OH) D levels, which emphasizes its immunomodulatory role in innate and adaptive immunity.

AUTO1-0675
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

IMPORTANCE OF ANTI-HMGCR ANTIBODIES ILLUSTRATED USING A CASE REPORT OF STATIN ASSOCIATED AUTOIMMUNE MYOPATHY

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Background

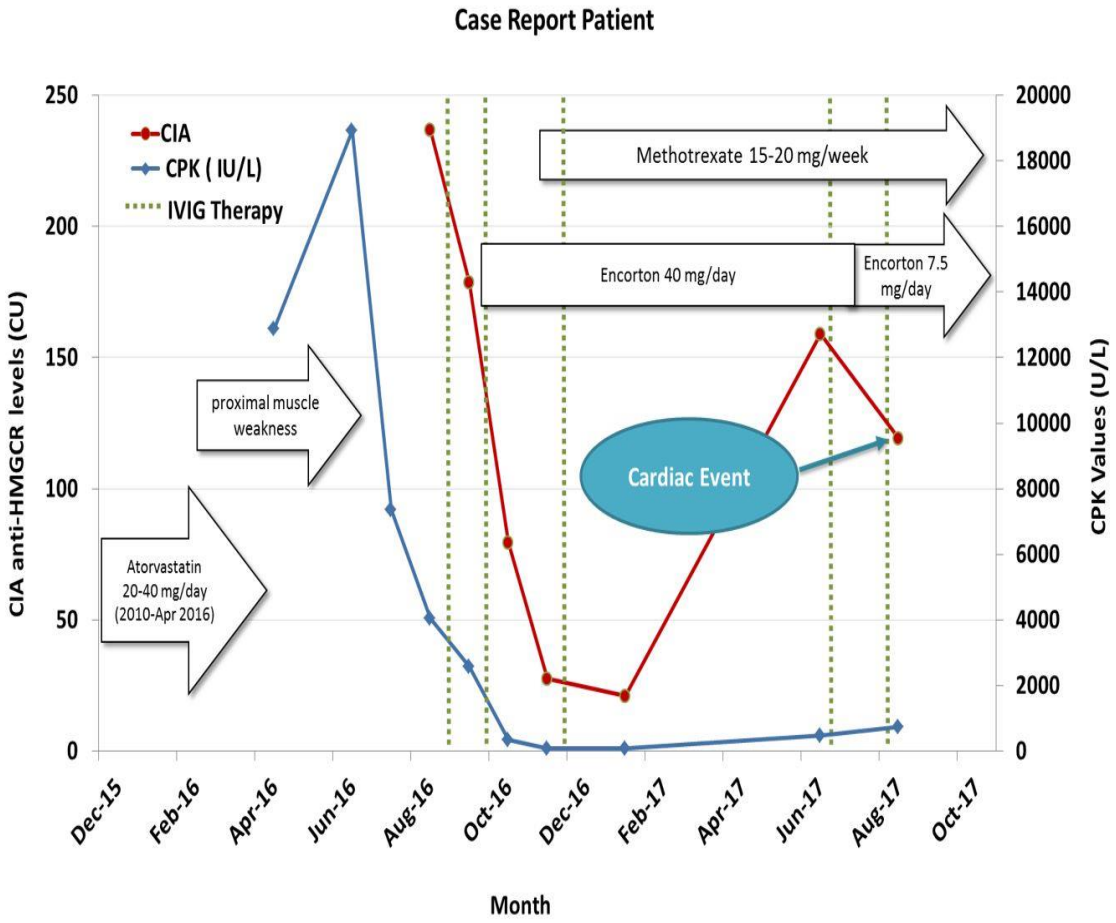
Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies have been recently described as a biomarker to differentiate frequent transient statin induced myopathies from immune mediated necrotizing myositis (IMNM) requiring immunotherapy. We aimed to report a case study of statin associated IMNM and assess the anti-HMGCR antibody levels during the course of the disease.

Method

A 69 year-old woman on statin therapy since 2010 was referred to the Immunology and Rehabilitation division of Malopolska Center for Rheumatology, with progressive muscle weakness since March 2016, myogenic muscle degeneration pattern in electromyography (EMG), and persistently high creatine phosphokinase (CPK) levels (>12,000 U/L). Anti-HMGCR antibodies were measured by QUANTA Flash HMGCR chemiluminescent immunoassay (CIA) (Inova Diagnostics, San Diego, USA).

Results

Histopathological picture of the patient was consistent with IMNM. The first blood draw in 2016 was high positive for anti-HMGCR antibodies. After receiving intravenous immunoglobulin (IVIG) therapy, the patient's muscle weakness subsided and anti-HMGCR antibody level decreased. In June 2017, while CPK were slightly and anti-HMGCR levels significantly elevated, the patient was not experiencing a worsening of symptoms. However, additional IVIG treatment was administered. In September 2017 the patient suffered a cardiac event resulting in death. High anti-HMGCR antibody levels were found at the time of relapse and catastrophic event (see figure).



Conclusion

A diagnosis of statin associated IMNM was established based on the patient's clinical and serological data. This is the first case report in which anti-HMGCR antibodies are shown to increase around the time of relapse which suggests their potential in predicting serious complications from statin associated IMNM.

AUTO1-0629
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

EVALUATION OF ANA, ANCA AND CRITHIDIA ON UPGRADED NOVA VIEW® AUTOMATED FLUORESCENCE MICROSCOPE

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Background

To evaluate the upgraded NOVA View®, a computer-aided automated fluorescence microscope for the three cell modules within and compare the performance to the original NOVA View® Automated Fluorescence Microscope.

Method

The study included samples of varying reactivity grades for all three cell types (ANA n=80, ANCA Ethanol set and Formalin set n=50, CLIFT n=30). All slides were run on the upgraded NOVA View® (Inova Diagnostics, USA) a total of 4 times and on the original NOVA View® (Inova Diagnostics, USA) a total of 4 times.

Results

The overall result observed was that upgraded NOVA View® had significantly lowered the scan time for every module. For ANA the scan time was decreased by 32%, for ANCA the scan time was decreased by 43% and for CLIFT the scan time was decreased by 30%. Also, both the upgraded NOVA View® and the original NOVA View® showed a high level of agreement (see table) with a Cohen's kappa ranging between 0.80-093 for all three cell types.

Substrate	Positive Agreement (%) (95% CI)	Negative Agreement (%) (95% CI)	Total Agreement (%) (95% CI)
ANA	94.9 (92.4 to 96.6)	87.6 (80.0 to 92.6)	93.5 (91.1 to 95.3)
ANCA Ethanol	98.0 (94.3 to 99.3)	95.1 (86.5 to 98.3)	97.2 (94.0 to 98.7)
ANCA Formalin	96.7 (92.5 to 98.6)	96.7 (88.6 to 99.1)	96.7 (93.3 to 98.4)
CLIFT	94.2 (87.1 to 97.5)	85.7 (72.2 to 93.3)	91.4 (85.3 to 95.1)

Conclusion

The upgraded NOVA View® Automated Fluorescence Microscope showed a decrease in scan time for all three modules (ANA, ANCA and CLIFT). This study also demonstrates that the upgraded NOVA View® system generates results equivalent to those of the original NOVA View® system.

AUTO1-0313
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PREVALENCE AND CLINICAL SIGNIFICANCE OF ANTI-ANNEXIN A2 ANTIBODIES IN RHEUMATOID ARTHRITIS

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Background

The synovial pannus involved in the joint destruction of patients with rheumatoid arthritis (RA) results from a neo-angiogenesis within the synovial membrane. Annexin A2 is involved in neo-angiogenesis and facilitates erosions in murine models of collagen-induced arthritis. The prevalence of IgG anti-ANXA2 (aANXA2) in RA patients is 10%, increasing to 14% in case of erosions. The objective of our study was to determine the prevalence of aANXA2 in RA patients and in patients with other inflammatory rheumatic diseases and to correlate aANXA2 with severe forms of RA.

Method

This was a retrospective, cross-sectional and monocentric study. Clinical data were collected in the patient's computerized medical record. aANXA2 was detected by ELISA.

Results

154 patients were included in the study: 48 RA, 25 spondyloarthritis (SA), 4 psoriatic arthritis (PsA), 12 Sjögren's syndromes (SS), 40 polymyalgia rheumatica (PMR), 25 other inflammatory rheumatic diseases, and 65 healthy controls. The prevalence of aANXA2 IgG was 20.8% in RA, 8% in SA, 8.3% in SS, 10% in PMR, 16% in other inflammatory rheumatic diseases, and 6.2% in healthy controls. In univariate analysis, there was a significant difference between RA patients and healthy controls regarding to age, gender and aANXA2 IgG. After a logistic regression analysis on age and sex, aANXA2 IgG remained associated with RA (Chi-square = 5.8705, p = 0.0154). There was no correlation between aANXA2 and severe forms of RA.

Conclusion

Our study showed an association between aANXA2 IgG and RA, with a prevalence of 20.8%.

AUTO1-0158
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

DIAGNOSTIC PERFORMANCE OF ANTIBODIES DIRECTED AGAINST CARBAMYLATED ANTIGENS IN A LARGE COHORT OF RHEUMATOID ARTHRITIS AND OTHER RHEUMATIC DISEASE SUBJECTS

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Background

Anti-citrullinated protein antibodies (ACPA) are important serological markers in the diagnosis of rheumatoid arthritis (RA) and have been incorporated in the classification criteria. Recently, antibodies directed against carbamylated antigens (anti-CarP antibodies) were identified in RA patients and studies have established their diagnostic and prognostic value. This study analyzed the diagnostic performance of anti-CarP using a single step assay in distinguishing RA from other autoimmune diseases.

Method

The study included sera collected from a large cohort of RA patients (n=640, all fulfilling the 1987 or 2010 ACR criteria) and controls (n=833 inclusive of 197 normal healthy individuals). Anti-CarP was measured using an ELISA based on carbamylated fetal calf serum (Ca-FCS, cut-off 20 units; research use only, Inova Diagnostics, San Diego, US). In parallel, anti-CCP antibodies (second generation) were tested using EliA CCP (ThermoFisher, Germany).

Results

Anti-CarP antibodies were present in 34% (216/640) of RA subjects with overall specificity of 78%. Anti-CCP was 66% sensitive for RA and yielded 97% specificity. When stratified by anti-CCP status, the prevalence of anti-CarP was 42% and 16% among anti-CCP positive and negative RA subjects, respectively. The prevalence of anti-CarP in various disease conditions ranged from 6% to 30% (see table). Diagnostic odds ratio

(DOR) for RA vs. the different control groups ranged from 1.2 to 8.2.

Disease group	Percent positives	Specificity	Sensitivity	LR pos	LR neg	DOR
Systemic lupus erythematosus	30% [110/369]	70%	34%	1.13 [0.94,1.37]	0.94 [0.94,0.91]	1.2 [0.9,1.6]
Sjogren`s syndrome	27% [17/64]	73%	34%	1.27 [0.833,1.94]	0.90 [0.77,1.06]	1.4 [0.8,2.5]
Autoimmune thyroid/hepatitis	26% [11/42]	74%	34%	1.29 [0.77,2.17]	0.90 [0.74,1.08]	1.4 [0.7,2.9]
Idiopathic inflammatory myopathies	20% [6/29]	80%	34%	1.69 [0.99,5.03]	0.83 [0.67,0.91]	2.9 [1.1,7.5]
Systemic sclerosis	15% [5/33]	85%	34%	2.23 [0.79,3.35]	0.78 [0.69,1.01]	2.0 [0.8,4.7]
Other autoimmune rheumatic diseases	14% [2/14]	86%	34%	2.36 [0.65,8.56]	0.77 [0.62,0.96]	3.1 [0.7,13.4]
Normal Healthy individuals	14% [28/197]	86%	34%	2.37 [1.66,3.40]	0.77 [0.71,0.84]	3.1 [2.0,4.7]
Primary Fibromyalgia	6% [5/85]	94%	34%	5.74 [2.43,13.52]	0.70 [0.65,0.76]	8.2 [3.3,20.4]

Conclusion

These data support the notion that anti-CarP antibodies are helpful in the setting of ACPA negative subjects with RA. However, clinicians should be aware that anti-CarP can be present in other autoimmune rheumatic diseases, particularly systemic lupus erythematosus (SLE).

AUTO1-0229
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

CLINICAL COMPARISON OF FULLY AUTOMATED SCREENING METHODS IN THE DIAGNOSIS OF ANA ASSOCIATED RHEUMATIC DISEASES

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Background

Detection of antinuclear antibodies (ANA) is important in the diagnosis of ANA-associated rheumatic diseases (AARD). Due to several limitations of ANA screening by the most commonly used method indirect immunofluorescence (IIF), fully automated solid phase assays (SPA) have been increasingly substituting IIF. The aim of this study was to compare several automated SPAs and an automated IIF system for ANA detection in a Spanish study population.

Method

The study included 149 patient samples from 92 AARD patients and 57 disease control patients. Samples were tested in parallel by chemiluminescent immunoassays (CIA), QUANTA Flash CTD Screen Plus and QUANTA Flash ENA7 (Inova Diagnostics, USA), ZENIT RA ENA Screen (A. Menarini Diagnostics, Italy), fluorescence enzyme immunoassay (FEIA, EliA CTD Screen, Thermo Scientific, Germany), DIASTAT ANA ELISA (ALPCO, USA), and IIF using an automated system (AESKUSLIDES on Helios IFA processor, Aesku Diagnostics, Germany).

Results

Good clinical performance was found for all ANA and ENA detection methods given the high odds ratios for predicting AARD (see table). The comparison between screening methods showed good overall agreement (total agreements ≥ 86.6%, Cohen's *kappa* ≥ 0.73). When analyzing discrepant samples between QUANTA Flash and EliA CTD

Screen, 10/12 QF+/EliA- were CTD patients and the one EliA+/QF- was a CTD patient.

Performance Characteristic	QF CTD	EliA CTD	DIASTAT ANA	IIF	QF ENA7	ZENIT RA ENA
Antigen composition	dsDNA, Ro60, Ro52, SS-B, Sm, RNP, Jo-1, Scl-70, Cenp-B, Cenp-A, PM/Scl, RNA Pol III, Ribo-P, Mi-2, PCNA, Ku, Th/To	dsDNA, Ro60, Ro52, SS-B, Sm, RNP, Jo-1, Scl-70, Cenp-B, PM/Scl, RNA Pol III, Fibrillarin, Ribo-P, Mi-2, PCNA	dsDNA, Histone, SSA, SSB, Sm, RNP, Jo-1, Scl-70, Cent A/B	N/A	Ro60, Ro52, SS-B, Sm, RNP, Jo-1, Scl-70	Ro60, Ro52, SS-B, Sm, RNP, Jo-1, Scl-70
Sensitivity in AARD (%)	93.5%	83.7%	81.5%	81.5%	76.1%	81.5%
Specificity in controls (%)	91.2%	94.7%	96.5%	96.5%	93.0%	87.7%
Odds ratio (OR)	149.1	92.4	121.3	121.3	42.2	31.5
Area under the ROC curve (AUC) (95% CI)	0.95 (0.92-0.99)	0.97 (0.94-0.99)	0.96 (0.92-0.99)	N/A	0.91 (0.86-0.96)	0.88 (0.82-0.93)

Conclusion

All SPA methods demonstrated reliable clinical performance while also having good agreement amongst them and in comparison to IIF. Most notably, QUANTA Flash CTD Screen Plus had the highest sensitivity in AARD patients which may be due to the optimal antigen mixture not found in the other methods.

AUTO1-0210
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

CLINICAL RELEVANCE OF PERSISTENT AND ISOLATED IMMUNOGLOBULIN-M ISOTYPE ANTICARDIOLIPIN ANTIBODIES IN THE BORDEAUX UNIVERSITY HOSPITAL

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Background

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent thrombosis and/or obstetrical morbidity along with persistent anti-phospholipid antibodies (APLa) including lupus anticoagulant (LA), anti-B2-glycoprotein 1 (anti-B2GPI) and/or anti-cardiolipin (aCL).

The aim of this study was to determined prevalence and clinical relevance of isolated and persistent positive immunoglobulin-M (IgM) aCL antibody in our medical center.

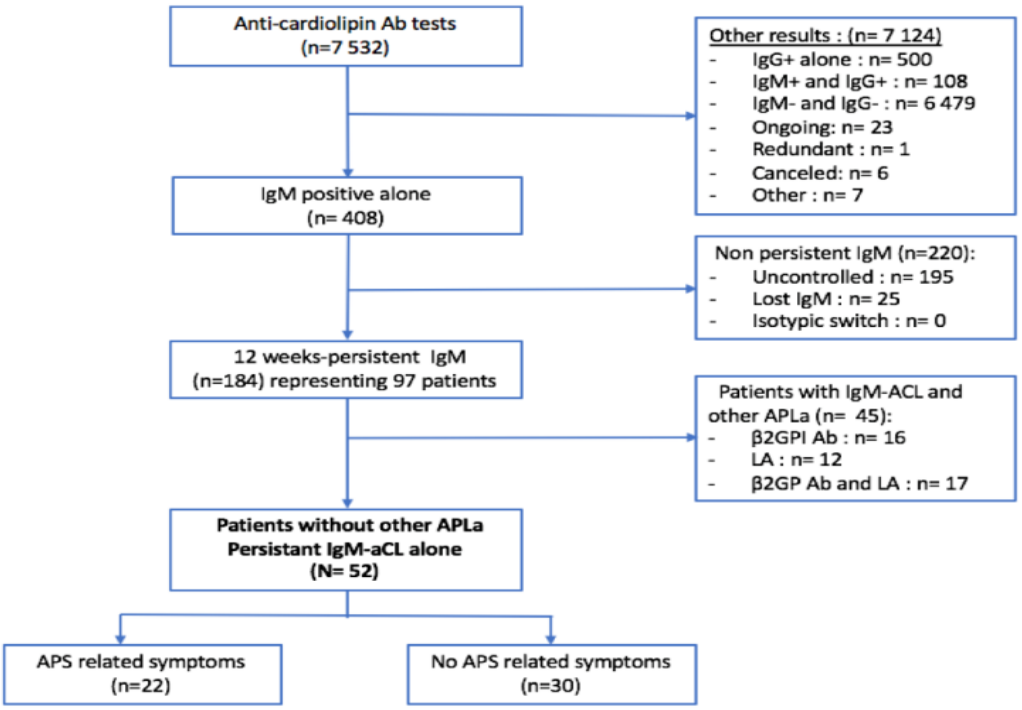
Method

We retrospectively analyzed 7 532 aCL tests (6 396 patients) between January 2015 to May 2017 and tested by chemiluminescent immunoassay (CIA) on the BIO-FLASH® (Inova Diagnostics, Ltd). We selected patients with a persistent and isolated IgM-aCL and clinical characteristics of such patients were analyzed.

Results

We detected 52 patients with a persistent and isolated IgM-aCL, representing 0.8% of the patients tested (Figure 1). The vast majority had levels of aCL below 50 UC. Twenty two of them (42.3%) have developed APS-related symptoms: 15 had a history of venous and/or arterial thrombosis, 6 had obstetrical events (miscarriage, pre-eclampsia, IUGR) and 1 a purpura. In 6 patients, these symptoms were associated with thrombocytopenia. The quantification of IgM-aCL antibodies was compared between the two group of patients (asymptomatic versus symptomatic) and was not statistically different (mean/standard deviation were respectively 40/22 and 53/65 UA for asymptomatic and symptomatic group).

Figure 1. Selection strategy among anticardiolipin antibodies tests.



Ab: antibodies; IgM: immunoglobulin isotype M; IgG: immunoglobulin isotype G; ACL: anticardiolipin; β2GPI : β2 glycoprotein I; LA: lupus anticoagulant; APLa: antiphospholipid antibodies; APS: antiphospholipid syndrome.

Conclusion

This study highlight that even a rare event, persistent isolated IgM-aCL are frequently associated to a history of APS-related symptoms.

AUTO1-0357
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

IFA SUBSTRATE PROCESSING, SCANNING AND ANALYSIS ON A FULLY AUTOMATED PLATFORM

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Background

Antinuclear antibody (ANA) testing by Indirect Immunofluorescence with HEp-2 cells as a substrate is a widely used method for autoantibody screening, however, the test is labor-intensive and subjective. Bio-Rad Laboratories, Inc. is developing a fully automated platform combining slide processing, imaging and analysis with Bio-Rad Kallestad IFA slides.

Method

Development of the pattern classifier algorithm was conducted in three phases. In Phase 1, Bio-Rad Liquichek controls established key features the classifier would associate with specific patterns (homogeneous, speckled, centromere, nucleolar, nuclear dots and cytoplasmic). Negative controls and serial dilutions of positive controls were used for defining the cut off intensity for positive and negative results. Phase 2 used prescreened patient samples to further define the classifier algorithms for pattern identification and positive/negative status. In Phase 3, ~1000 test-ordered ANA samples for IFA were processed and analyzed on both manual and fully automated platforms.

Results

Results as reported by the fully automated platform were compared to the manual reference and scored for accuracy in positive/negative status and pattern identification. Multiple fields of view (4x4 grid) were captured within each slide well and assembled into a composite mosaic image allowing for a comprehensive analysis by both the algorithm and the user. The fully automated IFA system determined the positive/negative status of the test-ordered samples and identified at least six important patterns for the ANA screen.

Conclusion

The new system offers increased standardization, traceability, improved workflow and objectivity for a traditionally labor-intensive and subjective process.

AUTO1-0469
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

CLINICAL USE OF QUANTITATIVE DETERMINATION OF SERUM ANTI-PHOSPHOLIPASE A2 RECEPTOR (PLA2R) ANTIBODIES IN PRIMARY MEMBRANOUS NEPHROPATHY

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Background

Membranous nephropathy (MN) is a main cause of nephrotic syndrome in adults and it is traditionally diagnosed by renal biopsy (RB). MN is most often primary, but it can be secondary to neoplasms, infections, drugs and autoimmune diseases. PLA2R is a transmembrane glycoprotein expressed in glomerular podocytes and it has been recognized as a major antigen target in primary MN (pMN). This study aims to evaluate the clinical use of quantitative determination of serum anti-PLA2R antibodies in the diagnosis and follow-up of patients with pMN.

Method

Observational, cross-sectional and retrospective study of patients with suspected MN followed in our hospital center. Quantitative determination of serum anti-PLA2R antibodies by enzyme-linked immunosorbent assay (EUROIMMUN, Lübeck, Germany) was compared with the histological findings of RB.

Results

A total of 69 subjects with a mean age of 59 years-old were included; 69.6% (*n*=48) were male and 30.4% (*n*=21) female. Among 19 histologically proven MN, 52.6% (*n*=10) had serum anti-PLA2R antibodies ≥ 20 UR/mL (mean 116.4 UR/mL, minimum 23.5 UR/mL and maximum 278 UR/mL) and 47.4% (*n*=9) had < 20 UR/mL. All 50 subjects without histologically proven MN also had serum anti-PLA2R antibodies < 20 UR/mL.

Conclusion

Our data suggest that serum anti-PLA2R antibodies seem to be an excellent biomarker in the diagnosis of pMN and a step-forward in establishing a serologic-based diagnostic approach, particularly if there are contraindications for RB. In addition, lower titters may identify patients undergoing immunological remission and higher titters may reflect worsening disease that is likely to require immunosuppressive treatment.

AUTO1-0779
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

CLINICAL USEFULNESS OF AUTOANTIBODIES TO M-TYPE PHOSPHOLIPASE A2 RECEPTOR (PLA2R) FOR DIAGNOSTIC AND MONITORING DISEASE ACTIVITY IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

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Background

This study aimed to assess the prevalence and the specificity of anti-PLA2R antibodies (Abs) in a cohort of Algerian patients with idiopathic membranous nephropathy (iMN) and to correlate them to disease activity parameters.

Method

We measured anti-PLA2R Abs using an immuno-enzymatic assay in the serum of 40 iMN patients; 09 with secondary MN and 10 with other forms of primary glomerular diseases.

Anti-PLA2R Abs were correlated with clinical parameters (proteinuria, serum albumin and serum creatinine) in patients with iMN.

In 6 iMN patients anti-PLA2R positive, Abs levels were assessed at various stages of clinical disease and correlated with clinical disease activity.

Results

Anti-PLA2R Abs were detected in 23/40 (57.5%) of iMN patients, but not in those with secondary MN or other forms of primary glomerular diseases producing a specificity of 100%.

In patients with iMN, the Abs levels correlated positively with proteinuria (r=0.6 , *p*= 0.0004). Abs levels were negatively correlated with serum albumin (r=0.56, *p*= 0.0008). No correlation was found between Abs levels and serum creatinine.

During the clinical course of the 6 anti-PLA2R positive patients. Abs levels correlated with cllinical status, which were high in the initial phase of active disease and decreased significantly during remission (*p*= 0.009).

Conclusion

These results suggest that PLA2R is a major target antigen in Algerian iMN and the detection of anti-PLA2R is a sensitive and specific test for iMN. Levels of circulating anti-PLA2R revealed a correlation with clinical disease activity. the detection and measurement of these Abs may provide a tool for monitoring disease activity.

AUTO1-0670
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

INTEREST OF THE QUANTIFICATION OF ANTIBODIES AGAINST HMGCR: A CASE OF NECROTIZING AUTOIMMUNE MYOPATHY

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Background

Necrotizing autoimmune myopathy (NAM) is a group of acquired myopathies characterized by prominent myofiber necrosis with little or no muscle inflammation. Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) were identified in statin-exposed and statin-non exposed patients with NAM. This study aimed to investigate the interest of the quantification of anti-HMGCR antibodies for the monitoring of one patient with NAM.

Method

Anti-HMGCR antibodies were quantified by a new chemiluminescence QUANTA Flash assay, utilizing BIO-FLASH instrument (Werfen).

Results

A 57-year-old woman was admitted for muscle pains, weakness and severe muscle wasting, with disability to walk. This patient was never on statin. On admission, the diagnosis of NAM was confirmed on the Creatine PhosphoKinase (CPK) at 20 000, the results of the muscle biopsy (muscle fiber necrosis) and the positivity of anti-HMGCR antibodies. The patient was then treated during 6 months with a combination therapy of Immunoglobulins and high doses of corticoid. Samples were collected before and after treatment and 6 months later. Anti-HMGCR titers were high at admission, and interestingly, a decrease of anti-HMGCR antibodies was observed after treatment. Moreover titers of antibodies were correlated with CPK values, electromyogram results and patients clinical response. We observed high titer of antibodies at diagnosis and marked decrease of antibodies when clinical improvement of the patient.

Conclusion

These results support the usefulness of the quantification of anti-HMGCR reductase antibodies as serological biomarkers for the diagnosis and also for the patient follow-up. Moreover, titers of anti-HMGCR could help for treatment decision.

AUTO1-0662
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

THE ROLE OF ANTI-DFS70 ANTIBODIES IN DIAGNOSTICS OF AUTOIMMUNE DISEASES

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Background

Antinuclear antibodies (ANA) are routinely detected in patients with systemic connective tissue diseases but some of them such as those directed against DFS70 antigen can be found preferentially in healthy individuals and patients with various inflammatory diseases.

Method

The aim of this study was to evaluate new diagnostic methods for the identification of anti-DFS70 antibodies in samples showing characteristic pattern of Dense Fine Speckled type of fluorescence.

The presence of ANA antibodies was tested in 52 patients and 15 healthy subjects by indirect immunofluorescence on Hep-2 cells. Patients were categorized according to the type of fluorescence image: homogeneous, speckled with or without positive metaphase chromatin staining and other type of fluorescence image. All the samples were then tested for the presence of ANA antibodies after immunoabsorption of anti-DFS70 antibodies (Inova Diagnostics). Furthermore, all samples were tested by immunoblot method containing DFS70 (Euroimmun). Anti-DFS70 antibodies were detected also by immunochemiluminescence (Inova Diagnostics).

Results

Patient samples with a typical homogeneous fluorescent pattern showed similar fluorescence image after saturation with anti-DFS70 (88%). Samples showing dense fine speckled type (with mitotic chromosomes condensed) pattern on HEp-2 cells were negative after the saturation with anti-DFS70 (82%) and anti-DFS70 antibodies were detected in 51% of samples by immunochemiluminiscence and in 58% by immunoblot.

Conclusion

We conclude from our study that both methods for immunoanalytical detection of anti-DFS70 antibodies are in a reasonable agreement (90.41%). Confirmation of the presence or absence of anti-DFS70 antibodies seems to be beneficial to exclude potential diagnostic errors particularly in homogeneous type of ANA immunofluorescence.

AUTO1-0522
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

DESMOSOMAL PROTEINS AUTOANTIBODIES IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

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Background

The diagnosis of Arrhythmogenic right ventricular cardiomyopathy (ARVC) has been developed on the basis of the fulfilment of major and minor criteria encompassing structural, histological, electrocardiographic, arrhythmic and genetic features of the disease. Mutations in the genes encoding desmosomal proteins, which are important in cell-to-cell adhesion, play a key role in the pathogenesis of ARVC. Mutated proteins include desmoplakin (DSP), plakophilin 2 (PKP2), desmoglein 2 (DSG2), and desmocollin 2 (DSC2) and might act as autoantigens.
Aim:To evaluate the potential role of desmosomal proteins autoantibodies as serum biomarkers in patients with ARVC.

Method

50 serum of ARVC patients and 39 serum of ARVC relatives were tested by a Dermatology Mosaic indirect immunofluorescence (IIF) assay (Euroimmun, Germany). Dermatology Mosaic contains: transfected cells (Dsg-1, Dsg-3, BP-230, Collagen VII), BP 180-NC16A-4X BIOCHIPs, salt split skin (SSS), monkey oesophagus and bladder mucosa (DSP, PKP and DSC).

Results

Sera from both patients and relatives were antibody-negative for Dsg-1, Dsg-3, BP-180, BP-230, Collagen VII. However sizable proportions of both sera from ARVC patients and relatives tested positive on SSS and on bladder mucosa (45% and 39% of patients, 47% and 35% of relatives respectively).

Conclusion

Our preliminary data suggest that the reactivity of ARVC sera on salt-SSS and bladder mucosa might be related to desmosomal protein antigens, such as DSP, PKP, DSC or other unidentified targets. Further work is warranted.

AUTO1-0524
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

RECOGNITION OF THE DENSE FINE SPECKLED (DFS70) PATTERN USING HEp-2/DFS KNOCK OUT SUBSTRATE AND IMPACT ON ANA SCREENING

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Background

Anti DFS70 antibodies produce a nuclear dense fine speckled immunofluorescence pattern on HEp-2 cells that can be confused as homogeneous or fine speckled. These antibodies target a 70 kDa antigen also known as LEDGF. Their presence was initially documented in patients with inflammatory conditions and in healthy subjects. Different commercial assays are available either to screening or to confirm DFS70 pattern on HEp-2 cells.
Aim: Evaluate a new method to screen DFS70 pattern (Menarini, Italy). This new IFA kit is able to screen and confirm the DFS70 pattern on HEp-2 cell in one step.

Method

122 samples from our routine laboratory with suspected DFS70 pattern and 25 DFS70 positive with CLIA method (INOVA, USA) were tested with HEp-2/DFS70 Knock-out IFA slide (Menarini Diagnostic, Italy). On these slides standard HEp-2 are mixed with HEp-2 with the psip1 gene knocked out (eHEp-2) in 1:9 ratio. Non engineered Hep-2 detect all autoantibody specificities.

Results

In 122 suspected DFS70 samples only 14 (11.5%) were confirmed on this new susbstrate. Among the 25 patients already confirmed, we recognized 22 samples as positive (agreement 88%).

Conclusion

Implementation of the newly HEp-2/DFS70 Knock-out IFA substrate as the first step of ANA screening may be a convenient option for a one step detection of both anti DFS70 antibodies and the other ANA pattern. Furthermore this method eliminate the need of specific confirmation assays.

AUTO1-1017
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ONE YEAR REAL-LIFE EXPERIENCE WITH ANTI-CN-1A AUTOANTIBODIES IN CLINICAL ROUTINE FOR MYOPATHIES

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Background

Antibodies against cytosolic 5' nucleotidase 1A (anti-cN-1A), also known as anti-Mup44, are found in a third of sporadic inclusion body myositis (sIBM) and in less than 5% of other myopathies and neuromuscular disease.

Method

136 consecutive patients with myopathy were tested for IIF ANA, ENA (CTD screen, Phadia), a line-blot assay for myositis specific and associated antibodies (Euroline Myositis 3, EUROIMMUN), an ELISAs for anti-HMGCR (INOVA) and anti-cN-1A (EUROIMMUN). Clinical data was retrospectively collected for patients positive for anti-cN-1A.

Results

6.6% (9/136) patients resulted positive for anti-cN-1A antibodies. 4 patients had a clinical diagnosis of sIBM (3 biopsy confirmed, 1 pending). The other 5 patients had five different diseases (namely, polymyositis, dermatomyositis, polymyositis/systemic scleroderma overlap syndrome, undifferentiated connective tissue disease and Sjogren's syndrome). Among anti-cN-1A positive patients, distal atrophy was significantly associated with a diagnosis of sIBM (Fischer's exact test, $p = 0.0476$). CK levels were elevated (mean 541±578 U/L, range 72-1765 U/L).

Conclusion

This real-life experience with anti-cN-1A antibodies highlights their supportive role in the differential diagnosis of myopathies. Despite low sensitivity, anti-cN-1A autoantibodies are highly predictive of sIBM, especially when used with an elevated pre-test probability, thus being of particular importance when bioptic specimens are not diagnostic.

AUTO1-0477
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

EVALUATION OF ANTI-RA33 ISOTYPES WITHIN AN EARLY RA COHORT

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Background

Early diagnosis of rheumatoid arthritis (RA) leading to effective treatment is essential to improve prognosis and to prevent disease progression. Anti-CCP2 antibodies and rheumatoid factor (RF) have a sensitivity of approx. 70% and less in early RA (~ 60%). Anti-RA33 IgG antibodies are known as specific biomarker, especially in early RA. Recent studies show an emerging role of all three anti-RA33 isotypes in diagnosis and prognosis of RA.
The aim of this study was to evaluate anti-RA33 isotypes IgA, IgG and IgM for the diagnosis of early RA and to examine the added value compared to anti-CCP2 and RF within an early RA cohort.

Method

The cohort includes in total 654 patient samples, 257 RA patient samples and 357 control samples; various autoimmune (n=128), non-autoimmune diseases (n=130) and healthy subjects (n=99). Sera were analysed for the presence of anti-RA33, anti-CCP2 and RF (each IgA, IgG, IgM) using the EliA™ platform (Thermo Fisher Scientific, Phadia GmbH, Freiburg, Germany).

Results

One third of RA patients were positive for anti-RA33 showing a diverse distribution of all three anti-RA33 isotypes within our cohort leading to little overlap between immunoglobulin classes. The combination of all three RA33 isotypes detects 20% of the seronegative RA patients and the specificity of each isotype is ≥95%.

Conclusion

The combination of anti-RA33 isotypes gave a considerable added value in the seronegative group and the isotypes show strikingly little overlap. To fully evaluate the importance of the different anti-RA33 immunoglobulin classes within the pathogenesis of RA further investigations are required.

AUTO1-1015
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

EVALUATION OF DIFFERENT APPROACHES OF ASSESSMENT OF ANTI-DFS70 ANTIBODIES AND POSSIBLE CONCURRENT ANA AUTOANTIBODIES

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Background

Detection of ANA antibodies is an essential part of routine testing in patients with clinical suspicion of an autoimmune disease. One of the patterns that might present a complication in conventional testing, is the anti-DFS70 pattern. Its presence is used rather as an exclusion marker in patients with suspicion of having systemic autoimmune rheumatoid disease. However, attention should be paid to the samples screened for ANA as anti-DFS70 positive or suspected, mainly for exclusion of other clinically relevant autoantibodies. These might be undetected using IIF test only, hidden behind usually bright anti-DFS70 fluorescence.

Method

We tested different approaches for confirmation of anti-DFS70 positivity and exclusion or confirmation of other underlying ANA. The methods used were: indirect immunofluorescence using HEp-2000 cells as ANA screening with subsequent testing for anti-DFS70 antibodies and/or other relevant ANA using anti-DFS Ab adsorption agent and IIF evaluation; slides with normal Hep2 cells in combination with DFS70 knock-out cells for IIF; anti-DFS70/LEDGF determination with ENA screen, anti-dsDNA and anti-nucleosomes assessment; determination of ANA (with anti-DFS70) using a line blot assay.

Results

All samples screened for ANA and evaluated as anti-DFS70 positive or with suspicion of anti-DFS70 were tested using methods described above. All the different approaches with their advantages and disadvantages in terms of sensitivity and specificity, price, hands-on time and laboratory response were evaluated.

Conclusion

The aim of our work was to propose an algorithm for testing screening-positive sera in order to reliably and effectively detect possible underlying ANA positivity in DFS-70 patients in our routine laboratory diagnostics.

AUTO1-0397
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

10-YEAR DYNAMICS OF CHANGES IN THE COMPOSITION AND NUMBER OF PERFORMED AUTOANTIBODY TESTS IN THE LARGE INDEPENDENT LABORATORY.

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Background

Aim of the study: analysis of trends in practical use of autoantibodies testing.

Method

Statistics (database of the Independent Laboratory INVITRO for the years 2006, 2011 and 2016).

Results

Group of autoantibodies tests /related autoimmune diseases	Number of available tests / number of requests / % of all autoantibodies requests / n/1000 of all lab tests		
	2006	2011	2016
ANA variants	2 /2802 /5.0 /0.48	3 / 16168 /5.8 /0.44	7 /58676 /7.7 /0.49
RA	1 /7159 /12.7 /1.24	2 /30710 /11.1 /0.84	5 /117328 /15.4 /0.98
APS	2 /8371 /14.8 /1.45	6 /25644 /9.3 /0.70	12 /46295 /6.1 /0.39
Vasculitis	0	2 /1617 /0.6 /0.04	8 /6143 /0.8 /0.05
Gastrointestinal	0	5 /4537 /1.6 /0.12	13 / 64790 /8.5 / 0.54
Liver	0	3 /3645 /1.3 /0.10	4 /6592 /0.9 /0.05
Skin	0	1 /48 /0.02 /0.001	6 /273 /0.04 /0.002
Nervous system	0	0	8 /9532 /1.25 /0.07
Endocrine glands	2/38117 /67.5/6.60	7 /188693 /68.1 /5.15	13 /442325 /58.1 /3.73
Heart, blood	0	3 /1772 /0.6 /0.04	4 /3546 /0.5 /0.02
Autoantibodies tests in total	7 /56449 /100/9.78	31 /276771 /100 /7.57	79 /760182 /100 /6.41

Conclusion

The number of available tests has increased more than tenfold during the past decade. Among requests for autoantibody testing the percentage of those associated with gastrointestinal autoimmune diseases (including celiac disease), RA, autoimmune neurologic disorders, has grown. The proportion of autoantibodies tests among all lab tests declined slightly.

AUTO1-0484
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). SERUM FREE LIGHT CHAINS (sFLC) ASSOCIATED WITH ACTIVE DISEASE.

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Background

In SLE the cell and tissue damage is mediated by antibodies.It presents a chronic course in which the flares alternate with periods of inactivity.There is a shortage of biomarkers for hyperstimulated B cell conditions commonly found in patients with SLE and the existant not always predict disease activity.We present a case in which sFLC was very useful to control a patient with SLE.

Method

Patient with 20 years SLE.First flare in 2013 with hypertension, proteinuria and face edema.August 2005:progressive edema,increased abdominal perimeter,proteinuria of 5g/24 hours,leukopenia and severe hypocomplementemia.Kidney biopsy(KB) detected a membranous glomerulonephritis.May 2010:new flare with proteinuria, pancytopenia and decreased C3, C4.March 2011:new flare with neurological and haematological involvement,proteinuria in the nephrotic range and decreased C3/C4,KB:lupus nephritis type IV.August 2015:new hematological flare.July 2017:new flare with renal involvement (creatinine 1.83 g/dL, hypocomplementemia,proteinuria,anemia and thrombocytopenia,hypertension KB:proliferative lupus nephritis,class IV.Necrotizing vasculitis.Disease monitoring is carried out through classical parameters:PCR,C3/C4,dsDNA.From 2010 sFLC is added.

Results

During follow-up,no significant changes were seen in PCR concentrations,C3/C4 remained below the reference values. There decreased values more pronounced when an flare occurs; dsDNA remains positive.Since 2010,follow-up is also made by sFLC.Mean ΣsFLC when there´s no activity:86.5 mg/L. ΣsFLC increased during disease activity ahead of the clinic symptoms.Also, ΣsFLC descend quicker remaining stable after flare and ahead of the clinical improvement,predicting the end of the disease activity.C3/C4 normalizes slowly.

DATE	Cr	PCR	Kappa	Lambda	∑FLC	Hb	PLATLETS	LEUC	C3	C4	PT24h	GSR	dsDNA
MAY10	0.86	<0.6	52.3	34.2	86.5	8.4	86000	2140	21.3	1.8		43	P
MARCH11	1.17	<0.6	86.2	43.2	129.4	9.6	115000	2110	22.5	3.7	0.63		P
SEPT15	0.82		142.0	25.9	167.9	9.3	98000	1330	24.5	4.1	0.11		
JULY17	1.83	1.0	175.0	37.1	212.1	9.5	71000	3760	19.4	1.66	3.39		P

Conclusion

ΣsFLC can predict disease activity quicker than classical parameters as well as recovery,probably due to the short half-life of sFLC.sFLC it´s an interesting marker of activity that complement the classic parameters.

AUTO1-0978
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANA TESTING: AN EASI-SURVEY ON THE DAILY PRACTICE IN RUSSIA

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Background

European Autoimmunity Standardisation Initiative (EASI) has shown already the diversity of ANA testing between 12 European countries and also within the countries, by using special questionnaire. Russian EASI Group repeated this study in Russia by using the same survey in order to analyze the responses and compare them with the others countries.

Method

12 laboratory centers have been involved, 5 from them are Federal Laboratory Networks, which cover the territories of all regions in Russian Federation. The questionnaire was developed and standardized in the Excel EASI. The questionnaire consists of 51 questions in 5 categories. Statistical analysis of the results was carried out.

Results

40% of the laboratories in RF are ISO certified. 28% of labs perform ANA testing by IIF. There is a big diversity in technique, measurement, titrations and reporting. The considerable variety has been found also for Anti-dsDNA and ENA measurement by different methods (ELISA, CLIFT, FEIA and others).

Conclusion

The understanding of this diversity should accelerate harmonization process not only in Russia, but also in others EASI countries, and serve as a nice base for the development of international recommendations for autoimmune diagnostics of SARD.

AUTO1-0251
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

COMPARISON OF THREE AUTOMATED AND A MANUAL RADIOIMMUNOASSAY FOR THE MEASUREMENT OF ANTI-TSH-RECEPTOR (TSH-R) AUTOANTIBODIES

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Background

Background:

Graves' disease (GD) is a major cause of hyperthyroidism in humans and characterized by the presence of autoantibodies against the thyroid-stimulating hormone receptor (TSH-R). The detection of anti-TSH-R autoantibodies in patient samples represents a diagnostic criterion for this autoimmune disease, and immunoassays measuring anti-TSH-R autoantibodies aid in the diagnosis of GD.

Aim:

In this study, the clinical performances of three different automated enzyme immunoassays for the quantitative measurement of serum anti-TSH-R autoantibodies were compared with a manual radioimmunoassay (RIA).

Method

Methods:

A serum collective comprising 77 untreated and treated GD patients, 97 Hashimoto's thyroiditis patients and 182 patients with other autoimmune and non-autoimmune diseases was analyzed using EliA™ anti-TSH-R, two additional automated anti-TSH-R assays from different manufacturers (Manufacturer 1 and Manufacturer 2) and a manual RIA. To compare the clinical performances of the three automated assays, their agreement and correlation coefficient with the manual RIA was determined.

Results

Results:

In this study, EliA anti-TSH-R showed the highest agreement (98%) and correlation (r = 0.91) with the RIA. In case of Manufacturer 1, both the agreement (96%) and the correlation (r = 0.90) were slightly lower than for EliA anti-TSH-R. While the agreement between Manufacturer 2 and the RIA was the same as for EliA anti-TSH-R, the correlation (r = 0.86) was the lowest.

Conclusion

Conclusions:

Based on the highest agreement and correlation among the tested automated anti-TSH-R assays with the RIA as the gold standard, EliA anti-TSH-R was found to aid in the diagnosis of GD patients.

AUTO1-0572
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

INCIDENCE OF ANTI-RODS AND RINGS AUTOANTIBODIES IN DISEASES OTHER THEN HEPATITIS C

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Background

Antibodies to rods/rings antibody (anti-RR) have been most commonly observed in hepatitis C virus patients after IFN/ribavarin therapy, and in rare cases in individuals without HCV infection. The aim of this study is to review reports regarding frequency of anti-RR antibodies in other diseases and to determine prevalence of simultaneously presence of other antinuclear antibodies.

Method

The study sample consisted of 3372 patient serum samples that were routinely tested for antinuclear antibody (ANA) together with control group of 361samples. Indirect immunofluorescence(IIF) on HEp-2 cells has been used for ANA detection (Euroimmun, Lubeck, Germany). Immunofluorescence AC-23 ICAP pattern was considered positive for anti-RR. All ANA positive samples were tested with AtheNA Multi-Lyte®ANA-II Plus (Zeus Scientific, USA) for eight autoantibodies.

Results

In study group 1901/3372(56%) samples were ANA positive with IIF and 35 samples were anti-RR positive, while in control group 149/36(41%) were ANA positive without anti-RR.

In the anti-RR group, only 3/35 samples were positive for specific antibodies, while in the control group, there were 70/149 samples positive for specific antibodies ($p<0.0001$).

Among group of positive anti-RR patients only one patient was HCV positive, four had liver lesions, ten patients with SARD and other with various diagnosis.

None of the patients were under antiviral therapy (IFN/ribavarin) while19 were on poli and monotherapy.**Conclusion**

Anti-RR autoantibodies can occur in patients without evidence of hepatitis-C virus infection which indicates that there is another undetermined etiology for anti-RR antibodies. Presence of anti-RR antibodies usually excludes other antinuclear antibodies.

AUTO1-0901
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANTINUCLEAR ANTIBODIES IN PATIENTS WITH CLINICAL SUSPICION OF AUTOIMMUNE DISEASE

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Background

Autoimmune diseases are characterized by the production of autoantibodies against own structures of nucleus and cytoplasm. AID´s incidence estimation is between 1-20/100,000 habitants per year, with a prevalence of 3- 5% in general population. Indirect immunofluorescence (IIF) is the reference method for ANA determination establishing expressiveness and pattern in HEp-2 cells. Antinuclear antibodies (ANA) are used for screening of Autoimnune disease. This study aims to determine the prevalence of expressiveness of ANA and their specific antigens in patients AID´s clinical suspicion and the agreement of IFI-ANA automated and IFI-ANA manual.

Method

This is a cross-sectional epidemiologic study carried out in 540 samples from patients with clinical suspicion of AID. Patient´s average age was 43.4 ± 16.7 years, with a prevalence of female sex (75.8%). An automatic diagnostic platform (HELIOS) was used to determine the expressiveness of ANA. Simultaneously, IIF manual was read by two trained observers to establish agreement between methods. Positive samples from automated system were subjected to qualitative detection of IgG (17 antigens ANA) using Immunoblot assay.

Results

The expressiveness of ANA-IIF was 27.9% (CI95% 24.1 - 31.7%), from which 30.9% positive expressiveness were from women and 17.24% in men ($p<0.05$). Mostly fine speckled patterns (35.76%) were observed. 31.8% of ANA positive patients (n=151) expressed some antibodies by immunoblot, being the most frequent the dsDNA (25%).The agreement between IIF manual and HELIOS was high (Kappa 0.79).

Conclusion

Identified ANA´s prevalence is comparable to other populations. A proportionality between the titles of ANA-IIF and the expression of antigens by Immunoblot was established.

AUTO1-0234
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

Sensitive and Quantitative Methods for the Determination of anti-CCP-IgG & RF-IgM in Chinese Rheumatoid Arthritis Patients on the HOB BioCLIA®1200 Automated Chemiluminescence Immunoassay Analyzer

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Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that affects about 0.4% of Chinese population. Two serological biomarkers, RF (Rheumatoid Factor)-IgM and anti-CCP (cyclic citrullinated peptide) IgG have been widely use to diagnosis in the early stage of RA and predictive of disease progression. Recently, the innovative BioCLIA® anti-CCP-IgG & RF-IgM kits, coupling with the fully automated and random-access BioCLIA®1200 chemiluminescence immunoassay system have been launched and evaluated.

Method

In this study, the analytical characteristics (LOD, precision, dilution linearity & intra/inter-assays) were evaluated. Total of 514 clinical samples were analyzed for anti-CCP-IgG/RF-IgM with both BioCLIA® and commercialized ELISA kits. The other group of 336 clinical samples (RA =205, non-RA= 131) were also tested and compared the individual & combined diagnostic performance.

Results

verall, the BioCLIA® kits performed good analytical characteristics. The data showed that BioCLIA® anti-CCP-IgG and RF-IgM performed the similar sensitivity (95.4%/ & 96.9%), specificity (98.3% & 99.1%) and total agreement (97.1%/& 98.2%) with ELISA. In RA samples, we found BioCLIA® kits had the clinical sensitivity (70.2%/ & 74.6%) and specificity (93.9%/& 50.4%); the combined diagnosis has the higher sensitivity (80.5%) and specificity (47.3%), which is in accordance with ELISA results (sensitivity, 71.2%/& 76.6%; specificity, 91.3%/& 48.9%; combined sensitivity/specificity, 82.0%/& 42.7%).

Conclusion

BioCLIA® anti-CCP-IgG & RF-IgM kits performed well analytically on the fully-automated, random-access BioCLIA®1200 system. Combined of BioCLIA® anti-CCP-IgG and RF-IgM kits showed higher sensitivity performance is a good clinical diagnosis indicator in the early stage of RA.

AUTO1-0236
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

Performance Evaluation of BioCLIA® Anti-GAD Antibody Kit in T1DM Chinese Patients

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Background

The autoimmune deficiency of the beta cells of the pancreas is the major cause of insulin dependent diabetes mellitus (IDDM). Anti-GAD antibodies are the most sensitive indicator for the high-risk group with Type one diabetes mellitus (T1DM). Recently, the anti-GAD kit has been developed in automated BioCLIA® 1200 system and used to estimate the risk of development of T1DM.

Method

The innovative BioCLIA® anti-GAD kit is a double antigen sandwich format assay. The analytical performances including dilution linearity, limit of detection (LOD), precision (intra-assay & inter-assay) were evaluated. 150 clinical samples were both evaluated with a commercial anti-GAD ELISA and BioCLIA® anti-GAD kit. The different samples type including T1DM (N=100), T2DM (N=150), systemic lupus erythematosus (SLE; N=20), rheumatoid arthritis (RA; N=20), healthy donors (N=100) collected from local Chinese hospitals were also evaluated.

Results

The performance evaluation of HOB BioCLIA® anti-GAD kit showed the more accurate and faster results with an extended working range and good reproducibility. Compared with the ELISA kit, we observed the comparable sensitivity (94%; N=47/50) and specificity (98%; N=98/100) between two kits. The clinical sensitivity and specificity of T1DM were 85% (N=85/100), and 96.5% (N=280/290), while the specificity for T2DM, SLE, RA, healthy donors were 96% (N=144/150), 100% (N=20/20), 100% (N=20/20), and 96% (N=96/100) respectively.

Conclusion

The anti-GAD kit on the BioCLIA® 1200 automated platform exhibits an excellent sensitivity, a wider measurable range and shorter reaction time compared with traditional ELISAs. Its serves as a promising and environmental-friendly alternative for IFA and ELISA assays in the detection of T1DM autoantibodies.

AUTO1-0268
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANTI-PKCE AB CAN BE A CANDIDATE FOR AUTOANTOBODY IN ANKYLOSING SPONDYLITIS.

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Background

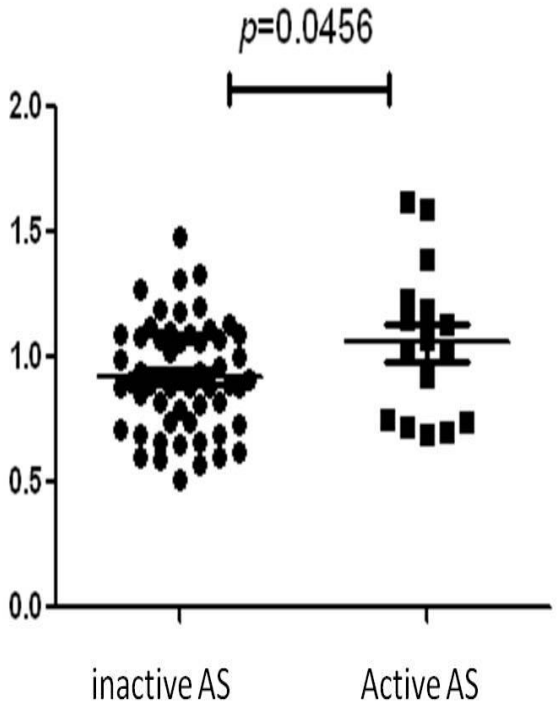
We chose anti-PKCE Ab as a candidate of autoantibody in ankylosing spondylitis (AS), which was an elevated autoantibody in microarray. PKCE was known as an enzyme associated with cell proliferation and apoptosis. There were some reports that this enzyme was hyperexpressed in breast cancer. In Inflammation pathway, this is also hyperexpressed.

Method

We checked anti-PKCE Ab in patients with AS by ELISA and analyze the results according to disease activity. We enrolled 120 patients with AS and 50 controls. The patients were diagnosed as AS by modified New York criteria. We checked anti-PKCE Ab by ELISA after coating with PKCE.

Results

There was no significant elevation of anti-PKCE Ab in AS (p=0.2584). In correlation analysis, anti-PKCE Ab was no correlation with ASDASESR, ASDASCRP and BASDAI. But in the patients who had more than moderate disease activity (ASDASCRP>1.3), anti-PKCE Ab was significantly elevated compared to in the patients who had inactive disease activity (ASDASCRP<1.3) (p=0.0456) (fig 1).



Active AS;
DASCRP>=1.3

Conclusion

Anti-PKCE Ab was significantly elevated in patients with active AS compared to inactive AS. We suggest that anti-PKCE Ab can be a candidate for autoantiboty of AS.

AUTO1-0069
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

LONG NONCODING RNA EXPRESSION PROFILE IN FIBROBLAST-LIKE SYNOVIOCYTES FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Long noncoding RNAs (lncRNAs) have recently received wide attention as key molecules that mediate a variety of physiological and pathological processes by regulating gene expression; however, knowledge of lncRNAs in rheumatoid arthritis (RA) is limited. Thus, we investigated the lncRNA expression profile in fibroblast-like synoviocytes (FLSs) from patients with RA and explored the function of abundantly expressed lncRNAs.

Method

LncRNA and mRNA microarrays were performed to identify differentially expressed lncRNAs in RA FLSs compared with normal FLSs. Quantitative polymerase chain reaction (qPCR) was used to validate the results, and correlation analysis was used to analyze the relationship between these aberrantly expressed lncRNAs and clinical characteristics. A receiver operating characteristic (ROC) curve was constructed to evaluate the diagnostic value of the lncRNAs identified.

Results

According to the gene expression profiles, 135 lncRNAs were differentially expressed between RA and normal FLSs. Furthermore, qPCR data showed that lncRNA ENST00000483588 was up-regulated and that three lncRNAs (ENST00000438399, uc004afb.1, and ENST00000452247) were down-regulated in RA FLSs. The expression level of ENST00000483588 was positively correlated with the level of C-reactive protein and the Simplified Disease Activity Index score. Moreover, the areas under the ROC curve were 0.85, 0.92, 0.97, and 0.92 for ENST00000483588, ENST00000438399, uc004afb.1, and ENST00000452247, respectively.

Conclusion

The results indicate that the dysregulation of ENST00000483588, ENST00000438399, uc004afb.1, and ENST00000452247 may be involved in the pathological processes of RA and that these lncRNAs may have potential value for the diagnosis and assessment of the disease activity of RA.

AUTO1-0457
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

LIVER AUTOANTIBODIES IN PATIENTS WITH MULTIPLE SCLEROSIS: IS THERE ANY REASON TO SCREEN MS PATIENTS WITH UNEXPLAINED ABNORMAL LIVER FUNCTION TESTS FOR LIVER AUTOANTIBODIES?

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Background

Abnormal liver function tests are frequently seen in patients with multiple sclerosis (MS) and their origin at times is attributed to the possible co-occurrence or the de novo induction of autoimmune liver diseases (AILD), namely autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC).

Aim: To assess the presence of AILD-related autoantibodies in a well-defined cohort of MS patients.

Method

133 MS (93 female) patients (102 RRMS, 27 SPMS, and 5 PPMS), mean age 42.7±11.9SD years, mean duration of disease 11.2 ±7.2 years. were studied. Autoantibody testing was performed by indirect immunofluorescence (IF) using triple tissue and HEp-2, a multiparametric line immunoassay detecting anti-LKM1(anti-CYP2D6), anti-LC1(anti-FTCD), soluble liver antigen/liver-pancreas(anti-SLA/LP), AMA-M2, and AMA-MIT3, PBC-specific ANA (anti-gp210, anti-sp100 and anti-PML), and ELISA for anti-F-actinSMA and anti-dsDNA antibodies.

Results

AIH-1 related anti-F-actin antibodies were present in 21 (15.8%), at relatively low titres (all but three of the SMA-VG pattern by IF); anti-dsDNA in 3 (2.3%), and anti-SLA/LP in none; AIH-2 anti-LKM1 autoantibodies in 1 (0.8 %, negative by IF), and anti-LC1 in none. PBC-specific AMA-M2 in 2 (1.5%), but negative for AMA-MIT3 and IF) and PBC-specific ANA anti-PML in 6 (4.5%), anti-sp100 in 1 (0.8 %) and anti-gp210 in 1 (0.8 %). Overall, 30/133 (22.6%) had at least one of the tested autoantibodies but only 4 (3%) had overt AILD (2 AIH-1 and 2 PBC).

Conclusion

Despite the relatively frequent presence of these autoantibodies either by IF or molecular assays, overt disease is rather infrequent discouraging autoantibody screening strategies of MS patients.

AUTO1-0640
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

BIOLOGIC THERAPIES IN RHEUMATIC DISEASES: DRUG AND ANTI-DRUG ANTIBODY LEVELS AND CLINICAL EFFICACY.

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Background

The aim of this study was to evaluate the relevance of drug and anti-drug antibody detection in the clinical management of patients with rheumatoid arthritis (RA) and spondyloarthropaties (SpA) in treatment with anti- tumor necrosis factor alpha (TNFα) biologics.

Method

The study included 192 adult consecutive patients treated for at least 6 months with adalimumab (ADA) or etanercept (ETN) or infliximab (IFX); patients underwent clinical observations in the Rheumatologic Unit of 5 Hospitals in Tuscany. Their demographic and clinical characteristics to calculate DAS28 and BASDAI scores were collected. Drug levels and anti-drug antibodies (anti-drug Ab) were evaluated immediately before drug injection or infusion.

Results

A total of 192 patients were studied: 62 receiving IFX, 64 ADA, and 66 ETN with a mean age of 57 years (range 18-86 years); the study group was composed of 51% women. Forty percent of the patients were affected by RA, 60% by SpA. Altogether, 81% of patients demonstrated therapeutic drug levels. Anti-drug Ab were found in 19% of patients taking IFX, 10 % taking ETN and 5% taking ADA. No significant correlation was found between anti-drug Ab presence and low drug levels, between anti-drug Ab and high DAS28 and BASDAI scores, as well as between low drug levels and high DAS28 and BASDAI scores .

Conclusion

Low drug levels were found in 19% of the rheumatic patients and there were not correlations with presence of anti-drug Ab or patient's clinical status.

AUTO1-0347
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

CLINICAL AND SEROLOGIC ASSOCIATIONS OF ANTI-MDA5 ANTIBODY: CASE SERIES OF THIRTEEN PATIENTS

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Background

Introduction: Anti-melanoma differentiation-associated gene 5 (MDA-5) antibody has been associated with three different phenotypes of dermatomyositis (DM): amyopathic dermatomyositis (ADM) and rapidly progressive interstitial lung disease (RP-ILD); ADM with typical skin manifestations; and antisynthetase syndrome (ASS)-like with mild ILD. There is lack of consensus regarding the diagnostic and prognostic value of the anti-MDA5 antibody.

Objective: To determine the clinical and serologic characteristics of anti-MDA5-positive patients.

Method

The study was performed in anti-MDA5-positive patients enrolled in a tertiary center database from January 2014 to July 2017. Anti–MDA-5 autoantibody was identified via immunoblotting, using a commercially available kit (Euroimmun®). Clinical and serologic data were collected retrospectively.

Results

Thirteen anti-MDA5-positive patients were found, four of them in pediatric age (between 7 and 17 years). Two of them presented with juvenile DM. Nine patients were adults: 7 female (67±8 years) and 2 male (49 and 67 years). Four adults had DM (two with ADM), one ASS, one Sjögren syndrome and one Autoimmune Hepatitis. Another four (two with DM, one with ASS and one with Sjögren) had ILD. Arthritis/arthralgia (n=5) and cutaneous manifestations (n=3) were the most frequently found in DM patients. With the exception of one patient, all were ANA positive.

Clinical and serologic characteristics of anti-MDA5-positive patients

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years)	13	17	49	75	14	67	70	64	72	56	58	74	7
Sex	F	F	M	F	F	M	F	F	F	F	F	F	M
Duration (years)	15	3	1	5	1	1	26	2,5	2	4,5	21	2,5	5
Heliotrope	-	+	-	-	-	-	-	NA	-	+	-	-	NA
Gottron	-	+	-	-	+	-	-	NA	-	+	-	-	NA
Raynaud phenomena	-	+	-	+	-	-	-	NA	+	-	+	-	NA
Arthritis/ Arthralgia	-	+	+	-	+	-	+	NA	-	+	+	-	NA
ILD	-	-	-	+	-	-	-	NA	+	+	+	-	NA
Malignancy	-	-	+	+	-	NA	-	NA	-	-	-	-	-
CCS	-	-	-	-	-	-	-	NA	-	-	-	-	+
Muscular involvement	-	+	-	-	-	-	-	-	-	+	+	+	-
Máx CK value (IU/l)	88	48	539	108	44	24	55	86	142	208	1895	187	<20
Máx aldolase (IU/l)	NA	14,4	6,8	5,1	7,6	NA	NA	6,8	NA	10,3	42,5	NA	NA
ANA titre	320	160	160	640	0	160	160	320	160	160	NA	640	80
ANA pattern	DFS	DFS	DFS	FG	NA	FG	FG	FG	FG	NH	FG	FG	DFS
anti-SSA	-	+	-	+	-	NA	+	-	+	+	+	+	-
Altered EMG	NA	NA	NA	-	NA	-	NA	NA	-	+	+	-	NA
Diagnosis	CCS	JDM/ ADM	ADM	ASS	JDM/ ADM	None	AIH	ADM	SS	DM	DM	None	CCS

ADM - amyopathic dermatomyositis; AIH - autoimmune hepatitis; ANA - antinuclear antibodies; ASS - antisynthetase syndrome; CCS - congenital cholestatic syndrome; CK - creatine kinase; DFS - dense fine speckled; DM - dermatomyositis; EMG - electromyography; F - female; FG - fine granular; ILD - interstitial lung disease; JDM - juvenile dermatomyositis; M - male; NA - non applicable; NH - nuclear homogeneous; SS - Sjogren syndrome.

Conclusion

MDA-5 is reported mainly in DM but also in other autoimmune diseases. Articular and cutaneous manifestations are the major features. ILD screening is recommended in all anti-MDA-5-positive patients.

AUTO1-0390
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PREVALENCE OF ANTI-DFS70 ANTIBODIES IN PATIENTS SUSPECTED FOR SYSTEMIC AUTOIMMUNE RHEUMATOID DISEASES (SARD) IN NORTH ESTONIA MEDICAL CENTRE

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Background

Most antinuclear antibody (ANA) patterns detected by indirect immunofluorescence (IIF) have diagnostic significance. But antibodies producing the dense fine speckled 70 (DFS70) pattern have been reported to be more prevalent in healthy individuals than systemic autoimmune rheumatic diseases (SARD). It has been mentioned in literature that positive DFS70 antibody is more frequent in women than in males and the prevalence also decreases in older age groups. We examined the prevalence of DFS70 in our hospital patients to prove this.

Method

We investigated 618 ANA positive samples of patients with suspicion of SARD. Among them we discovered 106 (21,7%) samples positive only for DFS70. None of these 106 patients had ANA-associated rheumatic disease (AARD). We used IIF (Hep2 cells, Euroimmun, Germany) for ANA screen and immunoblot (EUROLINE ANA Profile 3 plus DFS70, Euroimmun, Germany) for diligent ANA differentation. We devided these 106 patients by age and sex.

Results

Age (years)	Number of DFS70 positives	Male	Female
0,5 – 18	24 (22,6%)	6	18
19-30	21 (19,8%)	5	16
31-40	16 (15,1%)	4	12
41-50	11 (10,4%)	1	10
51-60	18 (17,0%)	2	16
61-70	10 (9,4%)	1	9
>70	6 (5,7%)	3	3
All	106	22 (21%)	84 (79%)

Conclusion

The prevalence of DFS70 seems to be higher in women than in men. But it needs further investigation, because women are more frequently suspected for SARD and tested for autioantibodies. The prevalence in younger age was not well proved in our study.

AUTO1-0939
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

INTEGRATION OF PLATELET MEMBRANE PROTEINS INTO LIPID BILAYER NANODISCS FOR THE DETECTION OF AUTOIMMUNE THROMBOCYTOPENIA

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Background

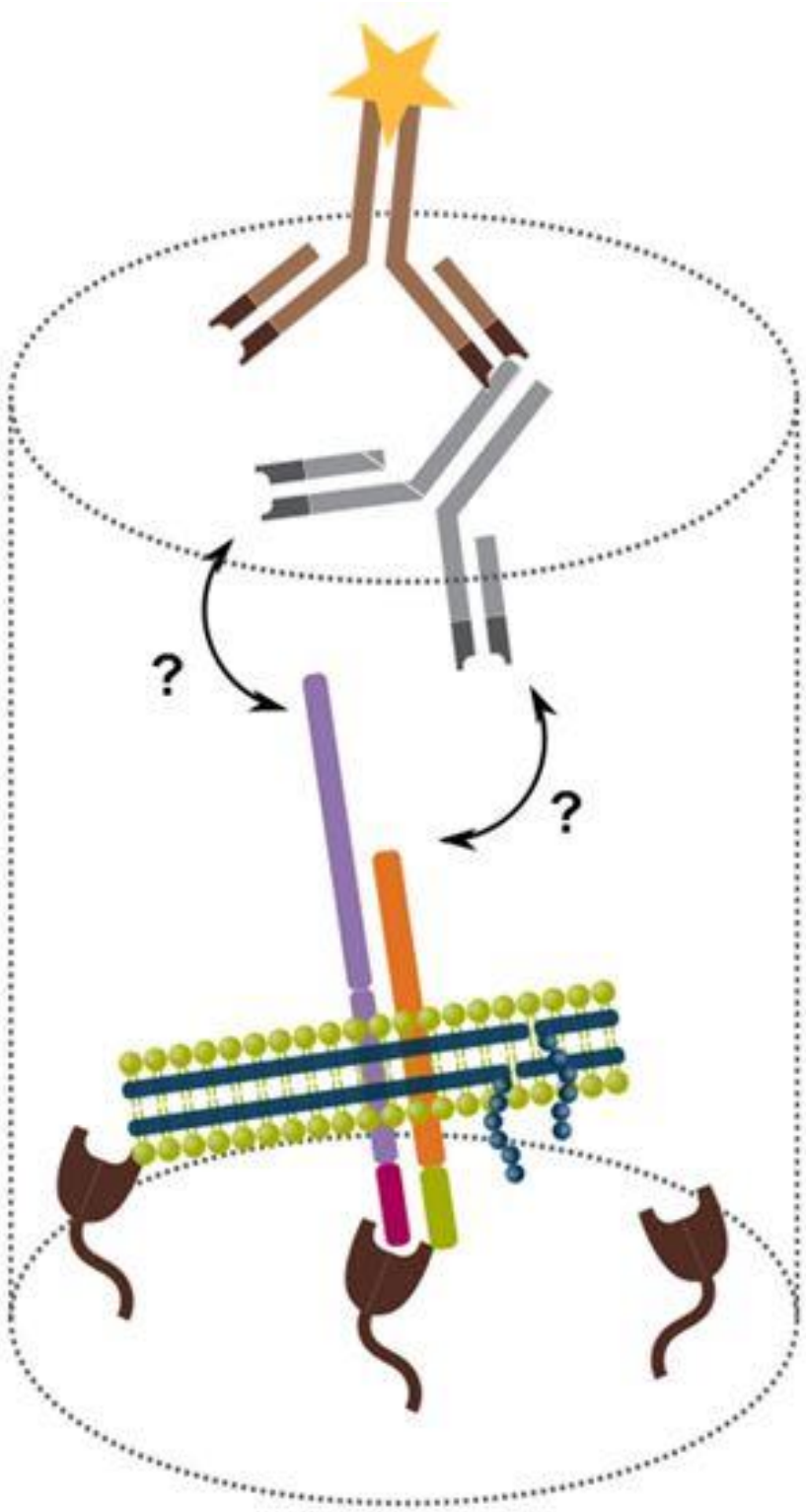
In autoimmune thrombocytopenia (AITP), platelets are destroyed by antibodies against different platelet membrane antigens, mostly against glycoprotein IIb/IIIa complex (GPIIb/IIIa). Although tests for patient anti-platelet antibodies are currently available, they have low sensitivities and a negative result does not necessarily rule out AITP. With the novel nanodisc technology, a sensitive and specific test for anti-platelet antibodies can be developed. Nanodiscs are self-assembled bilayers stabilized by synthetic membrane scaffold proteins, into which membrane proteins can be integrated in a native and functional form. Our aim is the detection of patient anti-platelet antibodies by ELISA using nanodiscs incorporating platelet membrane proteins.

Method

The platelet membrane protein GPIIb/IIIa was isolated from over-expressing HEK cell lines. As common protocols for nanodisc preparation are costly in terms of labor and time, including membrane isolation and long incubation steps, a simplified generation protocol was designed and tested. Resulting nanodiscs were examined with regard to size, shape and membrane protein incorporation.

Results

Nanodiscs were characterized and the incorporation of GPIIb/IIIa was verified. They were immobilized on a 96-well plate, which allowed detection of different antibodies against the glycoprotein complex. The reconstitution of membrane proteins allows for correct protein folding and a native lipid environment, thus increasing diagnostic performance of the test.



Conclusion

Our novel protocol allows fast and direct generation of nanodiscs from HEK cells and the confirmation of integrated platelet membrane proteins by ELISA. The next step will be the assay validation with authentic patient samples.

AUTO1-0481
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANTI-DFS70 ANTIBODIES IN PATIENTS WITH PSORIASIS AND PSORIATIC ARTHRITIS

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Background

Anti-DSF70 antibodies have been described in several diseases and in normal individuals but their clinical significance remains obscure. So far their presence in psoriatic arthritis (PsA) or in psoriasis (Ps) has not been studied, despite the fact that ectopic expression of DFS70 has been observed in keratinocytes, which suggests that it might be involved in psoriatic diseases. Our aim was to investigate anti-DSF70 antibodies in well-defined cohorts of Ps and PsA patients.

Method

A total of 70 patients (38 female, 54.3%, mean age 47.1±16.3 years) with Ps (n=36) or PsA (n=34), as well as 50 demographically matched healthy controls (HCs), were tested for the presence of anti-DFS70 abs by a line immunoassay.

Results

Reactivity against DFS70 was more prevalent in PsA patients (6/34,17.6%) compared to 1/36 (2.8%, $p<0.05$) Ps patients, and in 2/50 (4%) healthy controls ($p=0.056$, Fisher's exact test). Mean titres of anti-DSF70 abs in PsA, Ps and healthy controls were comparable. Anti-DFS70 antibodies were present in patients at baseline, as well as, following treatment with DMARDs or biologics.

Conclusion

This is the first study assessing and documenting the presence of anti-DFS70 abs in PsA. Their presence in PsA but not in Ps may bear a pathophysiological significance.

AUTO1-0270
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

KO
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Background

Determination of antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) using HEp-2 cells is still considered the gold standard test for screening of autoantibodies present in sera of patients with systemic autoimmune rheumatic diseases (SARD), thanks to its high diagnostic sensitivity. Nevertheless, its positive predictive value is low due to the relatively large amount of false positive results. Some of these have a dense fine speckled (DFS) pattern, which has been associated with several inflammatory diseases and is most commonly observed in individuals that do not have a rheumatic disease.

Our aim was to assess if in the new HEp-2/DFS70 Knock-out IIF test (Menarini diagnostics) the DSF70 is easily identified, still maintaining the detection of all the other ANA patterns.

Method

50 samples with known patterns (12 with DFS) were tested on both HEp2 and HEp-2/knock-out cells. The slides were evaluated by two expert-level observers, and all the images were acquired on a Zenit G-Sight (Menarini diagnostics).

Results

The 50 samples included 37 nuclear, 14 cytoplasmic and 4 mitotic patterns. The samples with an isolated DFS70 pattern were identified on the HEp-2/DFS70 Knock-out cells, and all the patterns were concordant on both HEp-2 substrates.

Conclusion

Since the patterns were similar on both cell substrates, and the DFS70 pattern can be accurately identified, the new HEp-2 KO cells may replace the ones we are currently using in our laboratory, avoiding unnecessary confirmatory tests in those samples who present this pattern.

AUTO1-0827
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

Near-Patient Anti-Nuclear Antibody Multiplex Testing Using Whole Blood for the Diagnosis of Connective Tissue Diseases in a Tertiary Care Center

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Background

Detection of anti-nuclear antibodies for the diagnosis of connective tissue diseases (CTD) often requires complex algorithms to obtain conclusive results which can delay the delivery of results.

The Maverick™ Detection System (Genalyte, Inc. USA) performs multiplexed detection of autoantibody binding events by measuring the shift in wavelength of ring resonance as the antibodies bind to the antigens on the surface above the rings. Just 10 µL of whole blood is required and results are obtained in less than 15 minutes.

Method

Whole blood from 205 consecutive patients followed-up at the Pitié-Salpétrière hospital (Paris, France) was analyzed on the ANA13PRI chip. 123 patients had systemic lupus erythematosus while others had other CTD. Comparisons were made with results obtained with routine procedures.

Results

The ANAPRI13 chip showed excellent total, positive and negative agreement when compared to the laboratory final conclusions for Sm, Scl-70, Jo-1, SS-A/Ro 60, SS-B, Centromere, Ku antigens with total, positive and negative agreement above 95%, and for PCNA above 92%. For RNP, total agreement was of 90%, positive was 100% and negative was 88.5%. For anti-nucleosome and anti-DNA the ANA13PRI displayed diagnostic performances close to commonly used ELISA systems.

For Ro52 and RibosomeP, the overall agreement and specificity were greater than 90%. Importantly, no diagnosis of CTD would have been missed by using the ANA PRI 13.

Conclusion

The Maverick detection system, which uses whole blood as the matrix and gives results in under 15 minutes, offers a reliable rapid diagnosis solution for the search of autoantibodies in CTD.

AUTO1-0470
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

IN PRIMARY BILIARY CHOLANGITIS, NEITHER MULTIPLE NUCLEAR ANTI-SP100 NOR NUCLEAR MEMBRANE GP210 AUTOANTIBODIES CORRELATE WITH ANTI-MITOCHONDRIAL ANTIBODIES

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Background

Anti-mitochondrial antibodies (AMA) are the diagnostic hallmarks of primary biliary cholangitis (PBC) being present in approximately 90% of patients with PBC, the two other disease-specific autoantibodies being multiple nuclear dots sp100 and nuclear membrane gp210 antibodies found in up to 25% of the patients. Several PBC patients may have detectable reactivities for AMA and con-current anti-sp100 or gp210 or both, a minority of those having all three reactivities.

Aim: To clarify the relation between AMA and PBC-specific ANA against sp100 and gp210.**Method**

Commercial and in house ELISAs were used to test for AMA-MIT3, anti-sp100 and anti-gp210 a total of 172 PBC patients. Antigenic preparations were based on a hybrid containing the major autoepitopic regions of the 3 mitochondrial antigens (MIT3), the M2 mitochondrial preparation, the core epitopic regions or extended polypeptide sequences of sp100 or gp210 nuclear autoantigens.

Results

Amongst 172 PBCs, 158(91.8%) were AMA-MIT3 positive including 34 AMA-MIT3/sp100 double positive (21.5%) and 38 AMA-MIT3/gp210 (24%) double positive (including 9 AMA-MIT3/sp100/gp210 triple positive). There was no correlation between AMA-MIT3 and anti-sp100, AMA-MIT3 and anti-gp210 or anti-sp100 and gp210 antibodies. Solid phase inhibition studies failed to document absorption of anti-sp100 or anti-gp210 by MIT3 antigen or vice versa.

Conclusion

PBC-specific ANA do not correlate with disease-specific AMA and their specific autoantigens are not targets of cross-reactive autoantibodies.

AUTO1-0421
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

VERIFICATION OF THE NEW CHEMILUMINESCENT ANTI-dsDNA METHOD

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Background

The aim of our study was the verification of the new chemiluminescent immunoassay (CIA) for anti-dsDNA (QUANTA Flash® dsDNA) on BIO-FLASH® Instrument (all Inova Diagnostics Inc, San Diego, USA), including comparison with currently used ELISA anti-dsDNA-NcX method (EUROIMMUNE AG, Lubeck, Germany).

Method

To evaluate assay precision, low (L) and high (H) commercial controls were run in triplicate for five days. Forty sera samples for comparison of CIA and ELISA were used. Due to the assay differences (cut off 100 IU/mL for ELISA and 27 IU/mL for CIA) results were categorized as positive/negative and Cohen's kappa test was used for agreement testing (criteria: kappa coefficient >0.60). Seventeen samples with positive anti-dsDNA by any method were additionally tested for confirmation with *Crithidia luciliae* indirect imunofluorescence (CLIFT) assay, (NOVA Lite® Inova Diagnostics Inc, San Diego, USA).

Results

Within-laboratory precision met the manufacturer declared criteria for L (mean 22.8 IU/mL, CV 3.61%) and H (mean 93.8 IU/mL, CV 5.14%) controls. Kappa coefficient was 0.75 (95%CI 0.54 – 0.95) with agreement of 87.5% between CIA and ELISA. CLIFT confirmed anti-dsDNA positivity in 11/17 (0.65) samples detected with BIO-FLASH; and in 9/14 (0.53) samples detected with ELISA.

Conclusion

Results showed acceptable precision of the BIO-FLASH CIA method and good agreement with ELISA method. Additionally, results of confirmatory test indicated CIA as method with higher specificity for anti-dsDNA than ELISA. Verification results along with the advantage of fully automated assay give advantage to CIA over ELISA method.

AUTO1-1023
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANTINUCLEAR ANTIBODY:CLINICAL ASSOCIATION AFTER 6 YEARS FOLLOW-UP

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Background

The purpose of this study is to make the follow-up of patients with positive antinuclear antibodies (ANA) and make the correlation between initial titers/patterns and progression to autoimmune disease (AID).

Method

During 2012, ANA tests of 1135 patients were evaluated. 214 who had ANA titer ≥ 1:160 and no diagnosis of AID were followed-up for a further 6 years. The final diagnosis were classified into AID, non-AID and non-confirmed

Results

Of 214 patients (163 females), 44 (21%) had ANA titer ≥ 1:640. ANA titer ≥ 1:1280 was associated with the female gender. The final diagnosis were: AID (33%), non-AID (24%) and no confirmed diagnosis in the remaining 91 (43%). No relationship between ANA pattern and the development of AID was found. Patients with high ANA titers were highly associated with AID (84 *vs.* 22%). The most common AID in this group was Systemic Lupus Erythematosus, followed by Sjögren's syndrome (SS) and Rheumatoid Arthritis (RA). RA was the most common AID in the low titer ANA group, followed by SS and autoimmune hepatitis.The mean time between first positive ANA and AID diagnosis was 1,2 years. Most of non-AID diagnosis had ANA titers <1:640 (96%). Liver and infectious diseases were the most common non-AID. 87 patiensts with low ANA titers and 8 with high ANA titers had no confirmed diagnosis in 6 years.

Conclusion

Patients with higher ANA titers are more likely to develop an AID. Disease progression can take a longer period to establish than the 6 years follow up.

AUTO1-0006
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

UVEITIS: DIAGNOSTIC WORK-UP. A LITERATURE REVIEW AND RECOMMENDATIONS FROM AN EXPERT COMMITTEE UVEITIS : DIAGNOSTIC WORK-UP; A LIETRATURE REVIEW AND RECOMMENDATIONS FROM AN EXPERT COMMITTEE

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Background

Diagnosis of uveitis is difficult. Etiologic investigations should take into account the epidemiology of uveitis and should focus on the most severe forms of the disease and those which can be treated. This study was undertaken to establish recommendations for the diagnosis of uveitis.

Method

Recommendations were developed by a multidisciplinary panel of 14 experts, including internists, ophthalmologists, and rheumatologists, and are based on a review of the literature and the results of the ULISSE study, which was the first prospective study to assess the efficacy of a standardized strategy for the etiologic diagnosis of uveitis. The following groups of patients are not included in these recommendations: children, immunocompromised patients, patients with severe retinal vasculitis, and those with specific eye diseases diagnosed by ophthalmologic examination only.

Results

Diagnosis should be guided by the medical history of the patient and physical examination. Serologic screening for syphilis is appropriate in all forms of uveitis. If uveitis is not diagnosed at this stage, investigations oriented by the anatomic characteristics of uveitis are proposed. These consist of assays for HLA-B27 (in unilateral acute anterior non-granulomatous uveitis), serum angiotensin-converting enzyme, interferon-gamma release, chest computed tomography (chronic uveitis), cerebral magnetic resonance imaging and anterior chamber tap with interleukin-10 analysis (intermediate or posterior uveitis in patients >40 years-old). Other investigations prescribed in the absence of orientation are usually unhelpful.

Conclusion

A strategy is proposed for the etiologic diagnosis of uveitis. The benefit of more invasive investigations remains to be determined.

AUTO1-0543
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ONCOSTATIN M RECEPTOR: POSSIBLE BIOMARKER FOR SYSTEMIC SCLEROSIS?

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Background

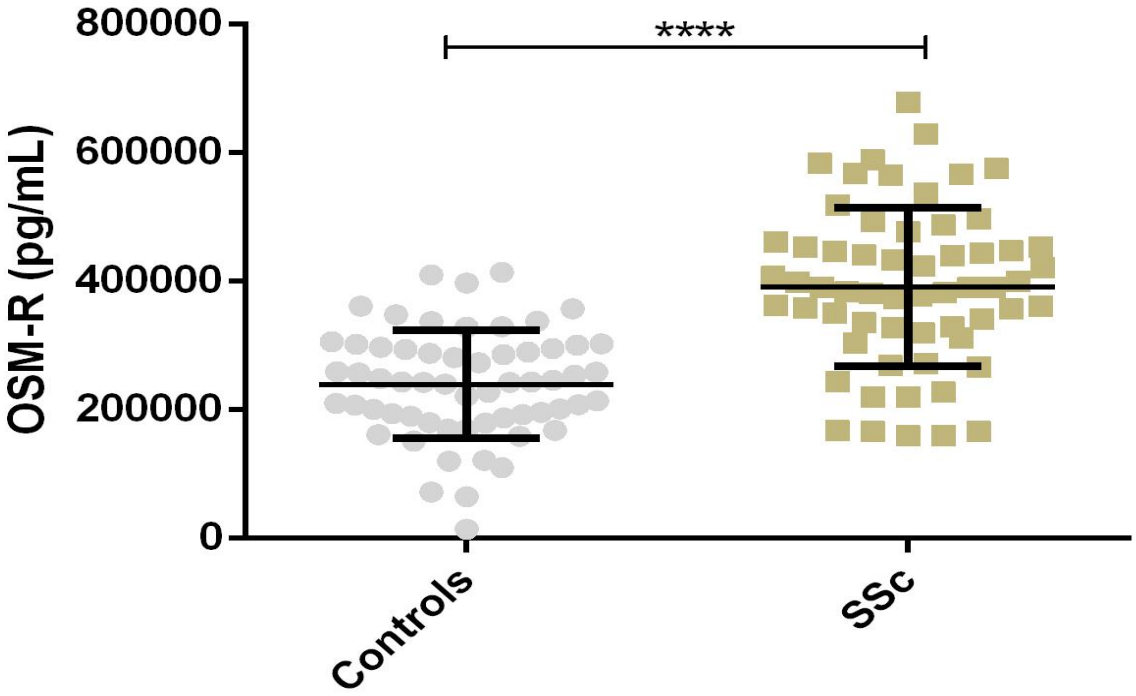
Systemic Sclerosis (SSc) is an autoimmune disease characterized by vascular damage, immunological dysregulation and fibrosis of the skin and internal organs. SSc presents dysregulated production of cytokines and their receptors that are involved in vascular damage and fibrosis. Oncostatin M (OSM) is a cytokine produced by activated T cells, monocytes and macrophages that performe functions in fibrotic process, such as increased collagen production and differentiation induction of myofibroblasts. This cytokine perform its functions through the signaling in its receptors. The type II receptor called OSM-R is more specific and performs a greater number of functions by binding to OSM. We evaluate serum levels of OSM-R in patients with systemic sclerosis and healthy controls and its association with clinical manifestations.

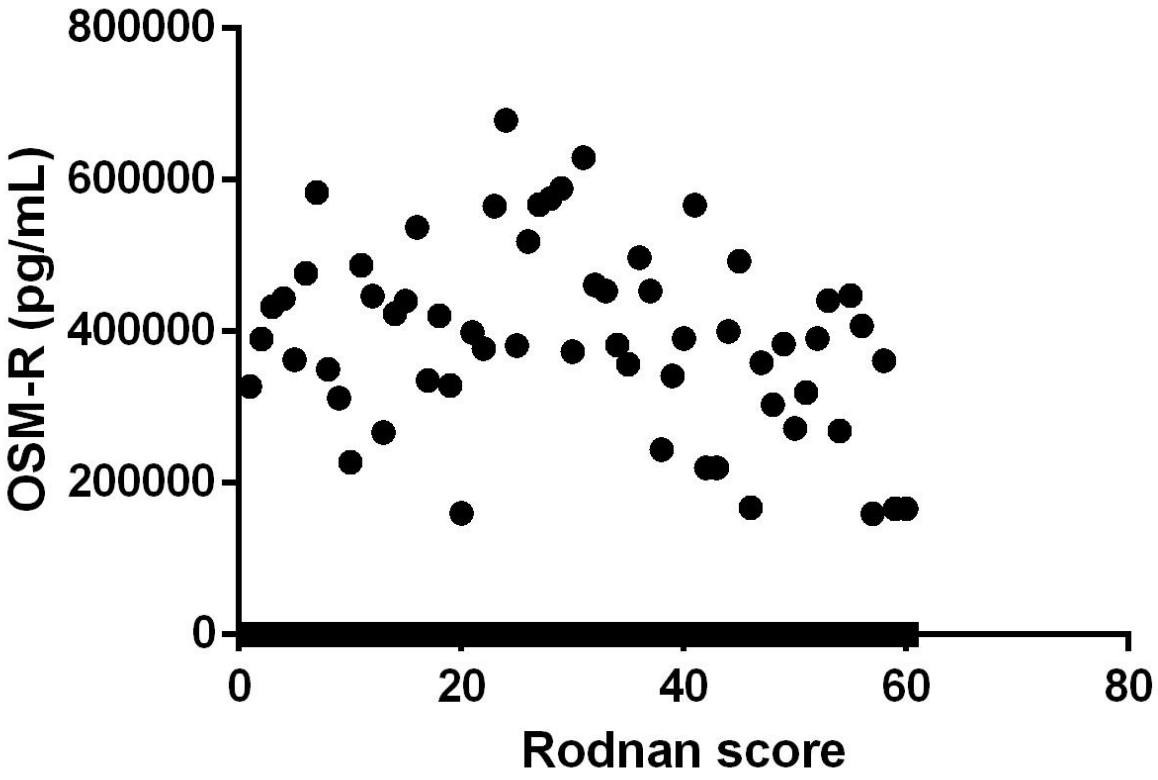
Method

Sixty SSc patients (mean age 45.57 +12.10) and sixty controls (mean age 56.28 + 14.49) were assessed. Clinical and laboratory parameters were recorded. OSM-R levels were measured by enzyme-linked immunosorbent assay (ELISA) and results were assessed by Student's "t" test and Spearman's correlation test.

Results

OSM-R serum levels were significantly increased in SSc patients compared with controls (mean 391.886 and 239.779,p<0,0001). There were negative correlations between OSM-R serum levels and cutaneous involvement assessed by Rodnan score (p= 0,035).





Conclusion

These findings show a significant increase in serum OSM-R levels in SSc patients when compared to controls, and suggest a possible association between serum levels of OSM-R and extent of cutaneous involvement in patients with systemic sclerosis.

AUTO1-0133
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

Autoantibodies to ribonucleoproteins (U1-nRNP) in Systemic Lupus Erythematosus (SLE) patients from Western India

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Background

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. Autoantibodies profile may help to predict clinical manifestations at evaluation. Anti-nRNP antibodies have been associated to Raynaud's phenomenon, myositis and absence of nephritis and MCTD. Clinical and serological associations of anti--RNP in SLE vary with ethnic and geographical distribution.

Aim : Prevalence of anti-RNP in SLE patients from Western India and their association with clinical and serological manifestations.**Method**

SLE patients (n=317) fulfilling the (2015 ACR/SLICC) criteria were enrolled. Anti-nuclear antibodies (ANA) (Biorad, USA), anti-dsDNA antibodies (AESKU, Germany) were tested by IIF. ANA specificities were tested by LIA-BLOT assay (AESKU, Germany).

Results

SLE cases (n=317) were recruited (2012-2016). Female to male ratio was 10.3 :1. Clinical manifestations of arthralgias &/arthritis were highest (53.9%), alopecia (46.4%), cuteneous (45.4%), oral ulcers (27.1%), renal (25.9%), hematological (14.8%), serositis (11%) and CNS involvement in 7.6% patients. Autoimmune overlap was in 53 patients (16.7%). Anti-nRNP antibodies were present in 94 patients (29.7%). Mean SLICC was higher (3.9+2.9) in anti-nRNP positive patients. Anti-nRNP antibodies was highest with renal manifestations (36.6%). Among SLE patients with overlap of other autoimmune diseases (RA, SS, Myositis, MCTD), SLE patients (n=28) had raynaud (8.8%), of which 11 patients (39%) had anti-nRNP antibodies. Anti-SSA (Ro 52,60) `and anti-Sm antibodies were highly associated (42.6%, 40.7% respectively) with anti-nRNP antibodies.

Conclusion

Anti-nRNP antibodies were significantly associated with malar rash and renal maniestations and anti-Sm and anti-SSA autoantibodies. Racial and environmental modulations may be responsible for variability found in these across the globe.

AUTO1-0104
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANTI-PEPTIDYLARGININE DEIMINASE TYPE 4 (ANTI-PAD4) AUTOANTIBODIES IN RHEUMATOID ARTHRITIS: CLINICAL AND BIOLOGICAL SIGNIFICANCE

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Background

Human peptidylarginine deiminase type 4 (PAD4), is a calcium-dependent enzyme catalysing citrullination that is involved in rheumatoid arthritis (RA) pathogenesis. A subgroup of RA patients display autoantibodies against this enzyme (anti-PAD4).

Method

We searched MEDLINE database for original articles focusing on anti-PAD4 antibodies published from 2001 to July 2017, to systematically address their diagnostic utility and provide an update of their clinical and biological implications in RA.

Results

Sensitivity of anti-PAD4 antibodies ranges from 18 to 50% among studies and is mainly affected by disease evolution of the RA cohorts, whereas their specificity is high (91-100%). Anti-PAD4 appear more frequently in established stages of RA, suggesting an epitope spreading origin. The strongest clinical association of anti-PAD4 in RA is with radiographic damage and progression, whereas their relationship with other clinical parameters such as disease activity or inflammatory biomarkers has not been robustly confirmed. Anti-PAD4 antibodies may have an inhibitory, neutral or activating effect on PAD4 enzyme depending on the epitopes they bind or their interaction with different PAD4 substrates.

Conclusion

Anti-PAD4 cannot be considered a useful early diagnostic tool, but their association with radiographic severity and progression highlights its utility as a severity biomarker. Anti-PAD4 may therefore help in selecting appropriate therapies for individual patients. Future studies in larger cohorts of patients are needed to confirm the utility of these autoantibodies, and to understand better the impact of anti-PAD4 on disease pathogenesis.

AUTO1-0163
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

THE CLINICAL RELEVANCE OF BORDERLINE RESULTS OF THE ELIA CTD SCREEN ASSAY

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Background

This study aimed to determine the clinical significance of borderline results of the Elia CTD Screen (ECS; Phadia, Thermo Fisher Scientific), a fluoroenzymeimmunoassay incorporating 17 recombinant human nuclear antigens.

Method

The medical records of 143 subjects with borderline ECS results (2.2% of 6458 consecutive samples tested for antinuclear antibodies, ANA) were retrospectively examined for the occurrence of ANA-associated autoimmune disorders and the association with the results of indirect immunofluorescence (IIF) and confirmatory assays for ANA.

Results

ANA-associated autoimmune disorders were diagnosed in 10 patients (7%) with SLE (n=5; 4 patients were prediagnosed and in clinical remission), polymyositis overlap syndromes (n=2), scleroderma, Raynaud's syndrome (n=1) and indetermined connective tissue disease (n=1). Most frequently, homogeneous and nucleolar IIF patterns were found. Positive ANA subsets were observed in 3 patients. Four patients were diagnosed with autoimmune liver diseases and yielded positive IIF in three and positive confirmatory assays in all
cases.

129 subjects had no ANA-associated disease. Within this group, 43 patients were IIF positive and most frequently showed speckled, unspecific nucleolar and only rarely homogeneous patterns. Positive ANA subsets were found in low concentrations near to the upper reference range in 18 subjects.

Conclusion

ANA-associated autoimmune disorders were observed in 10 (7%) of 143 subjects with borderline ECS and showed homogeneous or typical nucleolar patterns in IIF in the majority of these cases. Our findings suggest that borderline results of the ECS may be clinically relevant and support the concept of a parallel or sequential screening for ANA by both ECS and IIF.

AUTO1-0886
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

MANAGING CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS – SINGLE-CENTRE EXPIERIENCE WITH A RARE AUTOINFLAMMATORY DISEAS

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Background

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoimmune disease usually affecting children and young adults. The course of CRMO is characterised by recurrent episodes of inflammation within the skeleton. Due to non-specific symptoms the way to establish a proper diagnosis is long and based on excluding other diseases of the bone tissue. The aim of the study was evaluation of disease symptoms and treatment effects of CRMO patients treated in our Department.

Method

The study was conducted retrospectively on the group of 6 CRMO patients treated in our Department from June 2014 to August 2017. Medical histories of patients were precisely analysed including symptoms of the disease and results of diagnostic tests.

Results

In the study we have included 6 CRMO patients: 4 girls and 2 boys, aged 10 to 16 years. The most common CRMO symptom in our group was pain of the affected bone. In half of the cases the course of CRMO was multifocal. The most commonly affected bones were tibia (33%), vertebrae (33%) and bones of the pelvic girdle (33%). In 83% of cases we have observed mild elevations of inflammatory markers at the moment of diagnosis. In the treatment protocol NSAIDs (100%) and sulfasalazine (83%) were most frequently used.

Conclusion

Although CRMO is a rare autoimmune disease it should be included in the diagnostic protocols of chronic bone pain in children. Symptoms of CRMO may not be specific and diagnosis should be made after exclusion of other diseases such as bone tumours, bacterial osteomyelitis, juvenile idiopathic arthritis.

AUTO1-0942
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ASSESSING ANTI-dsDNA AND ANTI-CHROMATIN AUTOANTIBODIES IN THE SWISS SYSTEMIC LUPUS ERYTHEMATHOSUS (SLE) COHORT: PERFORMANCE OF THREE DIFFERENT COMMERCIAL ASSAYS

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Background

Anti-dsDNA and anti-chromatin autoantibodies are a hallmark for systemic lupus erythematosus (SLE) and can be detected by various methods. The aim of this study was to assess the clinical performance of different assays and to determine whether they differ in terms of association with specific organ involvement and accuracy to monitor disease activity (DA).

Method

Three assays relying on different methods were performed in serum samples from 175 patients of the Swiss SLE cohort which prospectively included adult SLE patients defined according to ACR criteria. Two assays detecting anti-dsDNA (QUANTA Lite dsDNA and QUANTA Flash dsDNA) and one detecting anti-chromatin antibodies (QUANTA Lite Chromatin) were compared. DA was assessed by SELENA-SLEDAI score having excluded the anti-DNA test result.

Results

The sensitivities were very similar among the assays: 48.6% for QUANTA Lite Chromatin, 48.0% for QUANTA Flash dsDNA, and 45.1% for QUANTA Lite dsDNA. Significant qualitative agreement ranging from 0.60-0.70 (kappa) and quantitative agreement ranging from 0.71 and 0.83 (Spearman's rho) were observed between the assays. The three assays were associated with DA assessed by SELENA-SLEDAI score, the higher association being achieved by QUANTA Lite dsDNA (p=0.018) followed by QUANTA Flash dsDNA (p=0.020) and QUANTA Lite Chromatin (p=0.029). Renal and haematological involvement were statistically associated with QUANTA Flash dsDNA (p=0.029 and 0.007 respectively) and QUANTA Lite Chromatin (p=0.044 and 0.002) positivity but not with QUANTA Lite dsDNA (p=0.065 and 0.18.

Conclusion

Our results stress the different performances of commercial assays designed to detect dsDNA antibodies each having preferential clinical associations.

AUTO1-0742
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

DNA METHYLOME AND SERUM PROTEOME ANALYSES IDENTIFY NEW BIOMARKERS OF PSORIASIS AND PSORIATIC ARTHRITIS IN MONOZYGOTIC TWINS

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Background

Psoriatic disease is a chronic inflammatory disorder spanning from skin disease (PsO) to psoriatic arthritis (PsA). The genetic background is insufficient to explain disease onset, and epigenetics, partially resulting from the interaction with the environment, represents a potential process modulating disease susceptibility. Moreover, proteomic analyses are crucial for the comprehension of the molecular mechanisms involved in the progression of the disease. In this frame, our aim is to analyze the epigenetics signatures and proteomics profiles of PsO/PsA in a cohort of monozygotic (MZ) twins discordant for the disease.

Method

We performed DNA methylation analysis (Infinium MethylationEPIC BeadChip), and transcriptome profile (Illumina TruSeq Stranded mRNA kit) in whole blood of MZ twins, whereas proteomic analyses (www.somalogic.com) were conducted on twins' serum.

Results

The epigenetics analysis identified 19 genes consistently differentially methylated and mostly involved in the pathway of TGF-β and IFN response. Pathway analysis of integrated methylome and transcriptome data evidenced an enrichment in "transcription regulation", "innate immunity", "ATP-binding" and, "Srp-dependent co-translational proteins", that may be involved in the psoriatic condition. Moreover, serum proteomics of PsO/PsA versus healthy twins showed a significant up/downregulation of 10 and 3 proteins, respectively, involved in the innate and adaptive immune response, DNA repair and DNA damage sensors pathways.

Conclusion

This omics approach allowed the identification of biological pathways and target proteins that could have a potential pathogenic role and may prove useful as disease biomarkers.

AUTO1-0743
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

A LARGE-SCALE PRTEOMIC APPROACH IDENTIFIED NEW SERUM BIOMARKERS ASSOCIATED WITH SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis (SSc) is an autoimmune disease associated with serum anti-nuclear antibodies (ANA) and anti-centromere (ACA), anti-topoisomerase I (ant-Scl70), and anti-RNA polymerase III antibodies, identifying patient subgroups. However, no reliable biomarkers can predict SSc susceptibility and internal organ involvement. Therefore, we aimed to identify serum protein biomarkers associated with SSc and interstitial lung disease (ILD).

Method

We analyzed serum samples of 3 patients with SSc and ILD and 3 patients with SSc and no ILD, and 4 healthy controls (HC). All subjects were women and age matched. Serum proteomics profiling was performed using the SOMAscan platform (SomaLogic, Inc., Boulder, CO, USA).

Results

Proteomic analysis identified 33 proteins which differentiated SSc from HC and 9 proteins which differentiate SSc patients with and without ILD. Compared to healthy controls, SSc cases showed an altered expression of proteins involved in extracellular matrix formation and cell-cell adhesion, angiogenesis, and lymphocyte recruitment, activation, and signaling, including interferon and IL-1 signatures, while an overall inhibition of markers of neutrophil function was noted. Patients with SSc and ILD manifested increased protein levels related to intracellular signaling and cell cycle, along with an increase of monocyte chemoattractants and ligands for the leukocyte adhesion compared to SSc without ILD. We further observed a decrease in B cell stimulating factor and IL-22 signaling in SSc and ILD.

Conclusion

Serum proteomic profiles can differentiate SSc from healthy controls and SSc patients with and without interstitial lung disease; moreover, our results identify biomarkers with a putative pathogenic significance.

AUTO1-0617
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANTI-RA33 (HNRNP-A2/B1) AUTOANTIBODIES ARE ASSOCIATED WITH THE THERAPEUTIC RESPONSE TO METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Besides the determination of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), anti-RA33 antibodies have some additional diagnostic value in patients with rheumatoid arthritis (RA) because they are also found in RF/ACPA negative patients. Since so far only IgG anti-RA33 antibodies have been determined it was the aim of this study to evaluate the prevalence, specificity and potential prognostic value of anti-RA33 IgG, IgM and IgA subtypes in RA.

Method

Sera from 255 RA patients, 258 disease controls and 100 healthy subjects were tested by a prototype anti-RA33 EliA® (Thermo Fisher Scientific). Therapeutic responses to methotrexate (MTX) were analysed in an RA inception cohort. To define therapeutic responses the simplified disease activity index (SDAI) and American College of Rheumatology (ACR) responses were calculated.

Results

Diagnostic specificity was >96% for all three anti-RA33 isotypes. Among the 255 RA patients, 11% tested positive for anti-RA33 IgG antibodies, 15% for IgM antibodies and 6% for IgA antibodies. Altogether, 62 patients (24%) had at least one type of anti-RA33 antibody and in 32 patients (13%), anti-RA33 was the only antibody specificity. Regarding responses to MTX therapy, the percentage of SDAI50 or ACR20 responders, respectively, was significantly higher ($p=0.034$ for SDAI50 and $p=0.005$ for ACR20) among anti-RA33 positive patients (with or without RF/ACPA) compared to anti-RA33 negative (but RF/ACPA positive) and anti-RA33/RF/ACPA negative patients.

Conclusion

Apart from their added diagnostic value, anti-RA33 antibodies seem to have also prognostic value for prediction of therapeutic responses to MTX treatment and might therefore become helpful tools in therapeutic decision making.

AUTO1-0034
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

MULTIPLEX LUMINEX A NEW DIAGNOSTIC APPROACH IN AUTOIMMUNITY: A REPORT EXPERIENCE FROM 2009 TO 2017

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Background

The centralization of requested laboratory tests, in particular specialist examinations, determined an increasing number of tests and critical points managed in the workflow of the laboratory.

Method

We started comparing Indirect Immunofluorescence (IIF) method on Hep-2 cells for antinuclear autoantibodies and Bioplex2200™ assay as new technology, collecting and analyzing 1205 serum samples with both methods.

Results

Agreement results were encouraging: 85.89% at IIF titre screen of 1/80, 87.47% at IIF titre screen of 1/160 and 92.61% at IIF titre screen ≥ 1/320, having greater sensitivity for Bioplex2200™ versus IIF for SSa, SSb, Sm, and RNP A autoantibodies. Since 2009 we have been employing Bioplex2200™ for ANA screen, and we have been maintaining IIF assay as second test and as first test only for particular clinical indications. This new workflow gives advantages on reproducibility, quality controls and on the whole autoimmune workflow. In 2010 and 2016-2017 we confirmed and deepened BioPlex ANA approach versus IIF approach, collecting and analyzing serum samples with clinical information and/or diagnosis.

Conclusion

The experience collected from 2009 to 2017, confirmed the advantages of using BioPlex2200 technology as first ANA test approach. To solve discrepancies for rare autoantibodies or unclear autoimmune diagnosis, we'll introduce immunodot tests.

AUTO1-0124
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

QUANTIFICATION OF IGG4 CONCENTRATION USING TURBIDIMETRY IN IGG4-RELATED DISEASE

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Background

Serum IgG4 measurement is included in all diagnostic guidelines for IgG4-related diseases (IgG4-RD), including type 1 autoimmune pancreatitis (AIP). The aim of this study was to confirm the clinical utility of IgG4 measurement in AIP using The Binding Site Group Limited (TBS) Optilite® turbidimetric analyser.

Method

Serum samples were obtained from 10 pancreatic cancer (PC) patients, 20 chronic pancreatitis (CP) patients and 30 AIP patients (49 male : 11 female, median age 67 years, range 37-86) diagnosed at Shinshu University Hospital, Japan. Serum IgG4 values >1350mg/L obtained using the Optilite® IgG4 assay were considered elevated. The Kruskal-Wallis and Mann-Whitney tests were used for statistical analysis.

Results

IgG4 concentrations were significantly higher in the AIP group (median, ranges): 3634mg/L (223-26432mg/L) for AIP; 492mg/L (139-1031mg/L) for PC; and 345mg/L (40-1108mg/L) for CP, $p < 0.0001$. 22/30 (73%) AIP samples had elevated IgG4 concentrations. None of the PC or CP patients had elevated IgG4. IgG4 levels among the subgroup of AIP patients with IgG4 <1350mg/L was significantly higher than CP patients (852 vs. 345mg/L, $p=0.009$) and approached significance for PC (852 vs. 492mg/L $p=0.06$). Using an IgG4 cut-off value of 800mg/L, but <1350mg/L, 6/8 (75%) AIP patients, 1/10 (10%) PC patients and 2/20 (10%) CP patients had concentrations above the cut-off.

Conclusion

Our study confirms the clinical utility of IgG4 measurements using the Optilite® analyser. Type 1 AIP exists as two forms, dependent upon increased production of serum IgG4 and IgG4 measurements may distinguish both forms AIP from other pancreatic diseases.

AUTO1-0980
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PLASMA CONCENTRATION OF AMINO ACIDS RELATED METABOLITES IN PATIENTS WITH SCLERODERMA

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Background

Concentration of plasma metabolites such as amino acids and its derivatives may provide indication for mechanisms of disease and suggest its biomarkers.

Method

This study aimed to evaluate changes in plasma concentrations of amino acids and metabolites in scleroderma. Plasma samples from 56 patients diagnosed with scleroderma were compared with 29 matched healthy controls. Liquid chromatography/mass spectrometry was applied for analysis of 36 metabolites.

Results

Analysis of plasma metabolite patterns revealed specific changes in scleroderma. Concentrations of NO synthase inhibitors: asymmetric dimethylarginine (ADMA) and N-Nitroarginine methyl ester L-NAME were increased in patients plasma by 20% and 8% respectively. Furthermore concentrations of hydroxyproline, betaine, glutamate, beta-alanine, 3-methyl-histidine, 1-methyl-histidine were increased by 14%, 20%, 19%, 20%, 24%, 36%, respectively while concentrations of taurine, tryptophan, methionine, aspartate were decreased by 7%, 20%, 10% and 11%, respectively in patients with scleroderma.

Conclusion

These results provides further evidence for involvement of endothelium in pathology of scleroderma. Such analysis of amino acid and related metabolite pattern may offer potential for diagnosis as well as for monitoring disease progression and therapy in scleroderma.

AUTO1-0577
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

THE MEASUREMENT/IDENTIFICATION OF DFS-70 AND ITS RELEVANCE IN AUTOIMMUNITY

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Background

Samples exhibiting a fine dense granular immunofluorescent (IF) pattern on HEp-2 substrate are frequently analyzed in the autoimmunity laboratory. Confirmation of their antigenic association to DFS70 / LEDGF is shown to be low in patients with systemic autoimmune rheumatic diseases, and have a high prevalence in apparently healthy individuals. However, they are frequently identified in patients with various inflammatory and malignant conditions. Through the evaluation of their clinical and biological importance, some studies have raised interest in DFS70 as a biomarker of the absence of multisystem autoimmune disease.

Method

The authors proposed to evaluate two methods in the identification of DFS70 (immunoblotting EUROLINE ANA Profile 3 plus DFS70 Euroimmun® and chemiluminescence QUANTA flash®DFS70INOVA) as well as its clinical importance.

Results

In a population of 70 patients, with GFD standard with titre ≥160, and with DFS70 positive by immunoblotting and negative ENA's, we obtained 50% positives by chemiluminescence.

Of these 70 patients, 90% are female; 13% are aged <15 years, and 59% are between the ages of 30 and 50.

19% of the patients had clinical manifestations related to connective tissue disease, and 13% had a history of infertility, spontaneous abortion and pre-eclampsia. The remainder had a history of stroke, hypertension or asthma.

Conclusion

The validation of a test with good sensitivity and specificity that allows the identification of anti-DFS70 antibodies may reveal utility in the exclusion of multisystem autoimmune disease and thus avoid the use of unnecessary tests.

AUTO1-0145
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

THE STABILITY OF RHEUMATOID FACTOR AND ANTI-CCP ANTIBODY IN ARCHIVED SAMPLES OF BLOOD

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Background

There has been increasing demand for analyzing a large amount of specimen at the same time and for stably storing those specimens for clinical research.The purpose of study is to evaluate the stability of RF and anti-CCP antibody after preserving the remaining samples for a long time and to determine the usefulness of the remaining samples that were kept for future research.

Method

At baseline measurement, rheumatoid factor was quantified with turbid immunometry and anti-CCP was measured by anELISA analyzer. all specimens were kept in a freezer where temperature monitoring was carried out for 24 hours to keep the temperature below -70 Celsius degree . 6 years later, the samples were measured by the same method of the baseline measurement.

Results

It was an average of 6.0 years (range: 5.6-6.1 years) for the samples to be stored at the biobank. We observed a slight decrease in concentration of RF and anti-CCP. There were significantly difference in concentration of RF and anti-CCP (Z= -5.10, p-value<0.001; Z= -3.81, p-value<0.001). The correlation between baseline sample and archived sample is strong (RF: ρ=0.973, p-value<0.001; anti-CCP: ρ=0.938, p-value<0.001).

Conclusion

Our results showed that serum concentration of RF and anti CCP antibody remain stable for up to 5 years at -70 Celsius degree. There was a slight decreased in the level overtime that was correlated with baseline value. These data indicated that the archived human samples in human cohorts could be used to examine for research and could be estimated according to the regression analysis.

AUTO1-0938
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

NANODISCS INCORPORATING FUNCTIONAL BETA-1 ADRENERGIC RECEPTORS AS NOVEL DIAGNOSTIC APPROACH FOR AUTOIMMUNE DILATED CARDIOMYOPATHY

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Background

Dilated cardiomyopathy (DCM) is a common cause of heart failure with a prevalence of 1:2500. Among genetic, metabolic and toxic factors inducing DCM, the presence of disease-driving anti-β1-adrenergic receptor (β1AR) autoantibodies was estimated as 25% to 75% in DCM patients. However, these autoantibodies could also be found in 10% of healthy controls. The association of anti-β1AR autoantibodies with the disease progression was proven by different analytical approaches and *in vivo* animal testing. Studies have shown that the removal of anti-β1AR antibodies as well as the interruption of the antibody-antigen interaction leads to a prolonged improvement of heart function in patients. To apply treatments targeting the autoantibody-β1AR interaction, the presence and impact of anti-β1AR autoantibodies in DCM patients must be examined. Until now, a reliable, standardizable diagnostic method is still not available.

Method

To enable the presentation of the native 3-dimensional conformational epitope, the β1AR was overexpressed in human HEK293 cells and reconstituted into nanodiscs. Nanodiscs are round slides of phospholipid bilayers stabilized by membrane scaffold proteins, which provide a native-like membrane environment for the incorporation of the correctly folded β1AR and stabilize it in aqueous solution for measurements with standard routine techniques.

Results

With this approach, immunoassays in ELISA and SPR formats were developed and optimized for the detection of anti-β1AR autoantibodies. The established ELISA assay allows a differentiation between anti-β1AR autoantibody-positive and -negative subjects in the analyzed patient collective.

Conclusion

Here, we present a novel *in vitro* diagnostic assay to support the diagnosis of anti-β1AR autoantibody-induced DCM.

AUTO1-0943
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

POSITIVE ANA ANTIBODIES – A PREDICTIVE FACTOR FOR SOME MANIFESTATIONS OF PATIENTS WITH JIA

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Background

The specificity of ANA autoantibodies in JIA has not been fully determined so far. Some studies have shown that ANA are associated with uveitis and correlate with disease progression. Furthermore, ANA positive patients have common characteristics of the disease. This study aims to investigate the implications of these autoantibodies in JIA, the association with uveitis and the favorable evolution of the disease.

Method

We followed patients suffering from JIA for a period of 2 years. ANA have been followed through immunofluorescence methods using a high performance Helios device. Titers higher than 1:40 after two determinations have been considered positive.

Results

From a total of 45 patients suffering from JIA, 28 have been ANA positive. 15 of the ANA positive patients presented an oligoarticular JIA, 8 of them presented a poliarticular JIA and 2 of them presented a systemic form. The most severe forms have associated iridocyclitis, 8 cases of the oligoarticular forms and 3 cases of the poliarticular forms. ANA titre has declined or has been no longer detectable if the disease had a favorable evolution. ANA positive patients from different ILAR categories had similar characteristics of disease such as onset age (earlier), higher prevalence in females, and presence of asymmetric arthritis or iridocyclitis.

Conclusion

1. Iridocyclitis is more frequent in ANA positive patients
2. Following ANA titre in evolution might be a criterion for assessing the evolution of the disease
3. ANA positive patients from different categories of JIA have similar characteristics of the disease

AUTO1-0801
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

COMPARISON OF DIFFERENT METHODOLOGIES FOR THE DETECTION OF AUTO ANTIBODIES IN SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

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Background

Compare the performance of different methodologies (IFA, ELISA and Blot) to detection of autoantibodies on a characterized cohort. The occurrence of autoantibodies is a common feature of autoimmune diseases therefore the detection of autoantibodies in the serum of patients is fundamental part of the clinical process. An ideal diagnostic test should have high sensitivity and specificity.

Method

250 samples from patients with systemic autoimmune rheumatic diseases (SARD) and 100 samples from healthy and disease controls were tested with ANA-17 PRO AESKUBLOT. In the SQ2 System were tested Sm, snRNP-C, SS-A, SS-B, Scl-70, U1-70, Jo-1 and Cenp-B by ELISA and HEp-2 ANA AESKUSLIDES in the HELIOS System.

Results

The IFA showed 95.4% sensitivity and 84.5% specificity. ELISA showed a higher specificity than IFA, and Blots showed an excellent correlation with both methods. The results were correlated with the group of SARD. Good qualitative agreement was found between the results.

Conclusion

The results demonstrated satisfactory analytical sensitivity and reproducibility in the routine autoimmune serology but the good performance and adequate interpretation depends on the algorithm used by the clinicians in each group of patients.

AUTO1-0288
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

Serum klotho concentration is inversely associated to the severity of nailfold capillaroscopic pattern in systemic sclerosis patients.

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Background

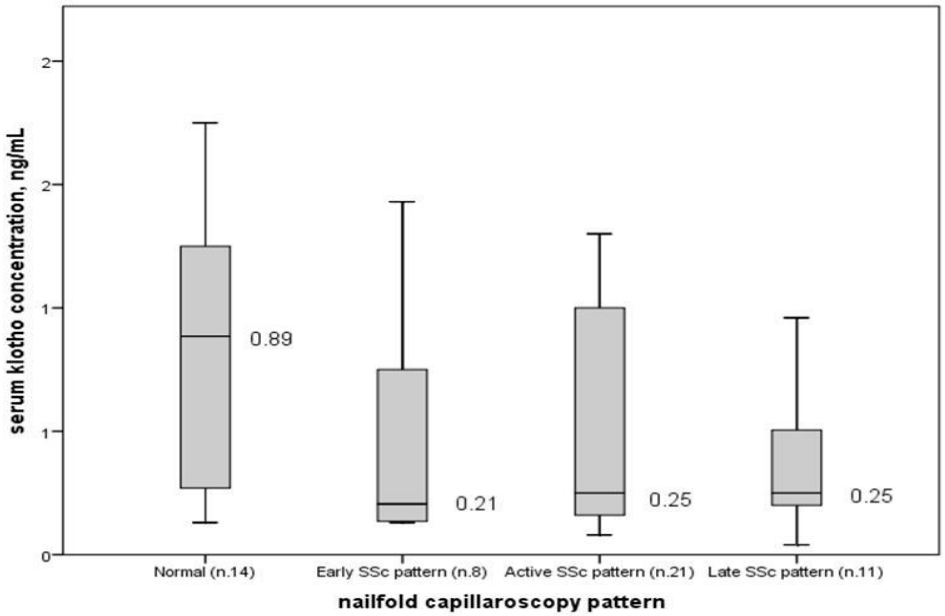
Klotho is a transmembrane and soluble glycoprotein presiding over vascular integrity. Previous studies demonstrated reduced serum klotho concentrations in systemic sclerosis (SSc) patients. Accordingly, a deficit of klotho may induce an impaired healing of digital ulcers, related to microvessel sufferance.
The aim of this work was to evaluate the association between serum klotho levels and nailfold capillaroscopic abnormalities in SSc patients.

Method

We retrospectively evaluated a cohort of 54 consecutive SSc patients (47 females, median age 68.0 years, IQR 18; median disease duration 11.0 years, IQR 7; 11 affected by diffuse form), according to EULAR/ACR 2013 criteria. Serum klotho concentration was determined on a serum sample through an ELISA test and nailfold capillaroscopy was contestually performed.

Results

Nailfold capillaroscopy showed a normal pattern in 14 patients, an early scleroderma pattern in 8 patients, an active scleroderma pattern in 21 patients and a late scleroderma pattern in 11 patients, according to the 2000 classification by *Cutolo et al*. Overall median serum klotho concentrations were 0.29 ng/mL, IQR 1. Regression analysis (ANOVA) showed an inverse association between serum klotho concentration and the severity of the capillaroscopic pattern ($p=0.02$; t -2.2284) which was not influenced by concomitant treatment. Logistic regression did not evidence any significant association between the risk of developing digital ulcers and nailfold capillaroscopic pattern, serum klotho levels or concomitant medications. The presence of avascular areas was significantly associated to calcinosis ($p=0.006$).



Conclusion

In line with previous studies, our results confirm the role of klotho in preventing microvascular damage, detected with nailfold capillaroscopy.

AUTO1-0306
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PRESENCE OF ANTI-TOPOISOMERASE I ANTIBODY ALONE IS NOT SUFFICIENT FOR THE DIAGNOSIS OF SYSTEMIC SCLEROSIS

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Background

The 2013 classification criteria for systemic sclerosis (SSc) provide 3 points (towards a 9 point diagnosis) for anti-topoisomerase I (anti-Scl-70) antibody positivity. In this study, we aimed to investigate the diagnostic relevance of anti-Scl-70 antibody positivity using a multiplex assay in patients under evaluation.

Method

Patients with positive for anti-Scl-70 antibodies (cut-off: >41 AU/mL) at the University of Utah over a period of 8 years had their charts manually review based on the 2013 SSc classification criteria.

Results

A total of 3331 unique patients evaluated during the period, 51 (1.53%) were positive for anti-Scl-70 antibodies with 5 lost to follow-up. Of the available anti-Scl-70 antibody-positive patients (n=46), 17 (37%) met the diagnostic criteria for SSc, 11 (23.9%) diagnosed with various lung diseases [sarcoidosis, pulmonary embolism, empyema, and constrictive bronchiolitis], 12 (26.1%) had immune-mediated disorders, and 6 (13%) no reported clinical diagnosis. All patients with SSc were positive for antinuclear antibodies (ANA) compared to those without (100% vs. 46.4%, $p<0.0001$). The median level of anti-Scl-70 antibodies was significantly higher in patients with SSc compared to those without [158 AU/mL vs. 60 AU/mL, $p<0.0001$). Using logistic regression, anti-Scl-70 antibody level of approximately 200 AU/mL was suggestive of a diagnosis of SSc.

Conclusion

A positive ANA and significantly elevated titers (>5x cut-off) of anti-Scl-70 may be predictive of SSc. The role of underlying lung pathology on the pathogenesis of developing a low titer anti-Scl-70 antibody with or without an ANA may warrant further study.

AUTO1-0307
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ASSESSMENT OF AN AUTOMATED INDIRECT IMMUNOFLUORESCENCE READER FOR THE DETECTION AND REPORTING OF ANTINUCLEAR ANTIBODIES

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Background

To evaluate the performance of an automated indirect immunofluorescence assay (IFA) reader for the detection and reporting of antinuclear antibodies (ANA).

Method

The study involved 151 patient (88 pediatric and 63 adult) serum samples received at ARUP Laboratories for ANA testing and a control cohort of 78 healthy adults. All samples were analyzed by both manual microscopy and the automated IFA reader (QUANTA-Lyser®/NOVA View®; INOVA Diagnostics, San Diego, CA) systems for ANA using HEp-2 substrate and IgG conjugate.

Results

The overall agreement between manual and automated was 95.6% for negative and positive ANA IFA results. Percent agreement for each of the five patterns (homogenous, speckled, centromere, nucleolar and nuclear dot) recognized by NOVA View® were 54.2, 41.9, 88.9, 50.0 and 20.0, respectively. Titer agreement was 86.8% at +/-1 titer and 97.1% at +/-2 titers.

Conclusion

The automated ANA IFA system showed good overall agreement with manual IFA, but requires an experienced technician to validate results, sometimes manually.

AUTO1-0430
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

VERIFICATION OF THE NEW CHEMILUMINESCENT SCREEN TEST FOR ANTIBODIES TARGETING EXTRACTIBLE NUCLEAR ANTIGENS (ENA)

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Background

We aimed to verify qualitative ENA7 (anti-Sm, anti-RNP, anti-Ro60, anti-Ro52, anti-SS-B, anti-Scl-70 and anti-Jo-1) screen chemiluminescent immunoassay (CIA), (Quanta Flash® ENA7) on BIO-FLASH® Instrument (all Inova Diagnostics Inc, San Diego, USA) and compare it with EUROLINE ANA Profile 3 plus DFS70 assay (line immunoassay comprising 16 antigens, including 7 aforementioned), (EUROIMMUNE, Germany, Lubeck).

Method

To evaluate assay reproducibility, negative (N) and positive (P) commercial controls were run in 20 replicates throughout 10 days (<10% wrong classified results allowed). Comparison study was performed on 38 sera samples. EUROLINE results was considered positive if any out of seven antibodies was positive. Methods agreement was tested with Cohen's kappa test (criteria: kappa >0.60). ANA indirect imunofluorescence (IIF) test, as a gold standard, was performed for all samples.

Results

Reproducibility study showed 100% correctly classified results. Kappa coeficient was 0.63 (95%CI 0.38 – 0.88), agreement 81.6%. Discrepances were observed in 7/38 samples: 4 were only ENA7 positive (positive ANA IIF in only 1) and 3 were only EUROLINE positive (highly positive Ro-52, SS-A and weak positive SS-B in first sample; weak positive Sm and SS-B in second; positive Ro-52 in third; negative ANA IIF in all 3).

Conclusion

Reproducibility of ENA7 test was excellent. Agreement of methods was weak (when kappa 95%CI is considered), in line with expected higher sensitivity of the screening test. Different sources of antigens could explain the positive results of confirmatory test while negative on ENA7. Based on our data we consider ENA7 as a reliable screening test.

AUTO1-0171
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

IS FAECAL CALPROTECTIN A USEFUL DIAGNOSTIC TOOL IN DIAGNOSING SPONDYLOARTHROPATHIES?

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Background

Spondyloarthropathies (SpA) are characterized by clinical and radiographic features on which the 'Assessment of SpondyloArthritis' (ASAS) classification criteria are based. The use of the ASAS criteria in the diagnosis of SpA is hampered by a low sensitivity of 79.5%. The aim of this study is to investigate the role of faecal calprotectin in the diagnostic process of SpA.

Method

Faecal calprotectin was quantified in adult patients with clinical suspicion of SpA. Patients were asked to discontinue intake of NSAIDs 2 weeks before sample collection. Patients previously diagnosed with inflammatory bowel disease were excluded. Three commercially faecal calprotectin assays (Quantum Blue Calprotectin, Bühlmann; QUANTA® Lite Calprotectin Extended Range, Inova Diagnostics; LIAISON® Calprotectin, Diasorin) were performed on each sample.

Results

In November 2017, preliminary results of 79 patients were analyzed, including 44 SpA patients. Faecal calprotectin levels were higher in the SpA group versus non SpA group, but diagnostic performance differed significantly between assays (Table 1).

In 34 of 44 SpA patients both radiology (MRI/radiography) and HLA-B27 results could be retrieved. Radiology showed sacroilitis in 41% of the patients and HLA-B27 positivity in 26% of the remaining, resulting in a combined sensitivity 67% for SpA diagnosis. Faecal calprotectin positivity increased this sensitivity, using a 97% specificity cutoff for SpA, up

to 71% (Bühlmann), 76% (Diasorin) and 74% (Inova).

Table 1. Diagnostic performance of different faecal calprotectin assays in SpA diagnosis

	Bühlmann		Diasorin	Inova	
Median [95 CI] in SpA (n=44) **Median [95 CI] in non-SpA (n=35)**	59.5 µg/g [15.0 – 300.0] 32 µg/g [15.0 – 157.0] *p*= 0.0147		24.4 µg/g [2.5 – 125.0] 11.5 µg/g [2.5 – 62.2] *p*= 0.0039	24.6 µg/g [2.8 – 110.2] 13.2 µg/g [3.8 - 60] *p*= 0.0248	
Manufacturer's cutoff **Sensitivity for SpA [95 CI]** **Specificity for SpA [95 CI]**	50 µg/g 55% [39-70] 71% [54-85]	200 µg/g 5% [0-16] 100% [90-100]	50 µg/g 27% [15-43] 97% [90-100] *P< 0.0001*	50 µg/g 14% [5-27] 97% [85-100] *P = 0.0313*	120 µg/g 0% [0-8] 100% [90-100]
Cutoff at 97% specificity for SpA **Sensitivity for SpA [95 CI]**	133 µg/g 18% (8-33)		50 µg/g 27% (15-43)	34 µg/g 32% (19-48)	
ROC's max. cutoff with 100% sensitivity for IBD* **Sensitivity for SpA [95 CI]** **Specificity for SpA [95 CI]**	148 µg/g 16% [6-30] 97% [85-100]		45 µg/g 30% [17-45] 94% [80-100]	40 µg/g 30% [17-45] 97% [85-100]	

** modified from Oyaert et al. (CCLM 2017) based on faecal calprotectin results of IBD (n=23) patients and non-IBD (n=62) patients*

Conclusion

The dosage of faecal calprotectin improves the diagnostic sensitivity for SpA, but the diagnostic performance depends on the analytical assay used. More data are necessary to confirm these hypothesis.

AUTO1-0463
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

ANALYTICAL PERFORMANCE OF THE SINGLE WELL TITER FUNCTION OF NOVA VIEW?: GOOD ENOUGH TO OMIT ANA IIF TITER ANALYSIS?

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Background

NOVAView (INOVA, USA) is an automated instrument for digital indirect immunofluorescence (IIF) antinuclear antibody (ANA) analysis. The instrument allows to estimate the endpoint titer based on the light intensity measured at the 1:80 screening dilution. We evaluated this 'single well titer' (SWT) function by comparing it with manual end point titer determination (ET).

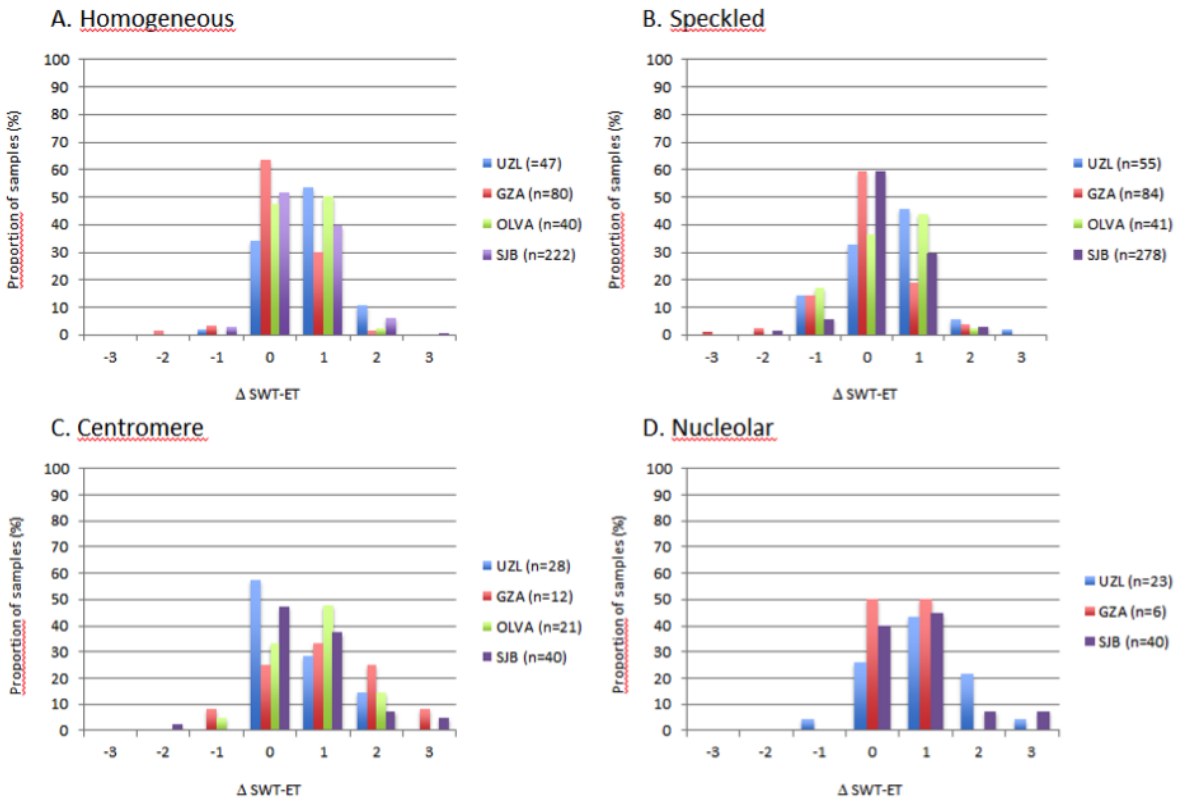
Method

Samples with an isolated homogeneous (n=389), speckled (n=458), centromere (n=101) and nucleolar (n=69) ANA IIF pattern were analyzed in four hospitals: University Hospital Leuven (UZL), Gasthuiszusters Hospital Antwerp (GZA), OLV Hospital Aalst (OLVA) and AZ Sint-Jan Bruges (SJB).

Results

When the results from the different laboratories were pooled, SWT and ET give identical results in 51.4%, 54.1%, 44.6%, and 36.2% of the samples with, respectively, a homogeneous, speckled, centromere and nucleolar pattern. An overestimation of 1 titer by SWT compared to ET was found in 40.1%, 31.0%, 36.6%, and 44.9% of samples with, respectively, a homogeneous, speckled, centromere and nucleolar pattern. In 15.9% and 17.4% of samples with, respectively a centromere or nucleolar pattern, the difference between ET and SWT was ≥2 titer steps (with higher values for SWT compared to ET). Figure 1 shows the breakdown of the results per laboratory.

Figure 1. Frequency histograms of the difference in single well titer and ANA IIF end point titer (serial dilution) for isolated homogeneous (A), speckled (B), centromere (C) and nucleolar (D) ANA IIF patterns.



Conclusion

When compared to ET, SWT tended to overestimate the titer in a substantial fraction of samples. The overestimation was 1 titer step difference in 36.0% of all samples, but ≥2 titer steps in 16.5% of samples with a centromere or nucleolar pattern.

AUTO1-0142
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

The Inova fecal calprotectin extraction device: an accurate and time saving alternative?

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Background

Within the scope of increased prevalence of inflammatory bowel disease (IBD) worldwide and the disadvantages connected to biopsy, there is a growing interest in efficient and accurate alternatives for IBD screening (1)(2). Fecal calprotectin is a stable biomarker correlating with the level of mucosal inflammation (3)(4). Several devices for calprotectin extraction were already marketed, but literature still designate the weighing method as golden standard, since other devices cause underestimation of results. Unfortunately, the weighing method is very time-consuming (5)(6).

The aim of this study was to investigate whether the device introduced by Inova can be a useful alternative.

Method

Therefore, fecal patient samples (liquid, semi-solid and solid) were extracted with the Inova buffer by using Roche (weighing method) and Inova devices and consequently measured with the BIO-FLASH® (Inova).

Results

The results demonstrated that sample consistency is important. Liquid samples should be pipetted (56µL) in the Inova device to give the same result as the weighing method. For solid samples, the executor should pay attention that >50% feces is removed out of the device's grooves. Notwithstanding, the results showed that the amount of feces sampled with the Inova device is vital for accurate results. When the amount collected is too low, a correction factor of 1.25 can be applied for solid samples. Alternatively, the procedure efficiency could be improved by sampling the feces by rotating the stick at least 5x powerful against the recipient.

Conclusion

These data proved the Inova device to be a promising alternative for the time consuming weighing method to extract calprotectin.

AUTO1-0434
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

COMPARISON BETWEEN THE DETECTION OF ANTI-CCP ANTIBODIES AND RHEUMATOID FACTORS (RF) IN THE DIAGNOSIS OF PATIENTS WITH POSSIBLE RHEUMATOID ARTHRITIS

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Background

Comparison of the detection of anti-CCP antibodies and RF in the diagnosis of rheumatoid arthritis (RA) in patients with a variety of joint symptoms.

Method

The survey is based on 282 patients who were admitted to the External Rheumatology Faculty of our hospital with symptoms and signs of inflammatory arthritis or polyarthralgia. Serum from all patients were examined for the presence of anti-CCP antibodies (ELISA)and RF (nebulometric method).

Results

77 patients were diagnosed as RA (ACR Criteria, 1987) while 205 patients were suffering from various rheumatic diseases, 47 of 77 RA patients were found positive for anti-CCP (62%) and 49 for RF (64%).. In the remaining groups of patients diagnosis included spondylarthritis (n = 37), Sjogren's syndrome (n = 30), undifferentiated synovitis (n = 29), systemic rheumatic diseases (n = 29), various arthritis (n = 22), SLE (n = 19) and other (n = 15). Anti-CCP were found in 4% and RF in 18% of the above cases.

Conclusion

In a population of Greek patients investigated for a variety of joint symptoms, detection of anti-CCP antibodies is accompanied by a similar sensitivity (62% vs. 64%) but by much greater specificity (96% vs. 82%) compared to RF, to diagnose RA. These results are consistent with international literature and justify the introduction of detection of anti-CCP antibodies in daily clinical practice.

AUTO1-0438
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PRESENCE OF ANTINUCLEAR ANTIBODIES IN PATIENTS WITH POSITIVE ANTI-CCP ANTIBODIES

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Background

To study the frequency of positive antinuclear antibodies (ANA) in patients with diagnosed rheumatoid arthritis (RA), who had not suffered by collagen disease and who had not been positive in anti-CCP antibodies (anticyclic cittrullinated protein antibodies), a new laboratory marker of RA.

Method

The material of our study consists of 76 patients with diagnosed RA, all of them being positive in anti-CCP antibodies. Serum presence of antinuclear antibodies (ANA) was studied with enzyme immunoassay ELISA (MEDICON) and indirect immunofluorescence method using Hep-2 cells (BIOSNA). Serum samples with ANA screen >0.9 index using ELISA method and titers of1/80 were considered as positive.

Results

33 of 76 of the patients (43.4%) were ANA screen positive and 34 (44.7%) were positive using the immunofluorescence method with a titer1/80. The staining pattern in the positive ANA samples was mostly homogeneous (82.3%).

Conclusion

None of the patients with positive ANA did present positive results in any of the individual specific autoantibodies (anti-ds-DNA, anti-RNP, anti-Sm, anti-CEN, anti-Jo-1). The frequency of positive ANA was higher in patients with onset disease. The presence of antinuclear antibodies in serum samples of patients with RA (as well as other autoantibodies) non specific for the disease, advocates over the polyclinic activation of B-lymphocytes.

AUTO1-0448
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PRESENCE OF INCREASED LEVELS OF ANTITHYROID ANTIBODIES IN THYROID DISEASES

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Background

The aim of the study was to compare the presence of increased levels of anti-Tg and anti-TPO antithyroid antibodies, in patients with thyroid diseases.

Method

120 patients with hyperthyroism,84 patients with chronic Hashimoto's thyroiditis and 51 patients with hypothyroism were the screening sample. The method that was used for the determination of the anti-Tg and anti-TPO antibodies was the Microparticle Enzyme Immunoassay (MEIA) using ABBOOTT's Architect analyzer.

Results

From the total of the 120 patients with hyperthyroism, 45 individuals showed increased levels of one or both of the antithyroid antibodies (37.5%). 62 patients out of the 84 with Hashimoto's thyroiditis (73.8%) and 16 (31.37%)out of the 51 patients with hypothyroism, showed increased levels of one or both of the antithyroid antibodies (anti-Tg and anti-TPO).

For the record, 28 patients with Hashimoto's thyroiditis were in the acute phase of the disease and all of them (100%) showed increased levels of antithyroid antibodies.

Conclusion

In the present study we noticed that: 1. Increased levels of antithyroid antibodies are detected in patients who suffer either from hyperthyroism or from Hashimoto's thyroiditis or hypothyroism. 2. The individuals that suffer from hypothyroism show the lowest percentage of increased levels of anti-Tg and anti_TPO antibodies, while the sufferers from chronic Hashimoto's thyroiditis show the highest percentage.

AUTO1-0451
DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY

PROGNOSTIC FACTORS FOR THE APPEARANCE OF AYTOIMMUNE ANTIBODIES AGAINST CYCLIC CITROOTINE PEPTIDES IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background

To investigate the correlation of the presence of aCCP, with clinical, laboratory and social characteristics of patients with early RA.

Method

From January 2012 to December 2016, 135 patients with early RA were diagnosed and subsequently followed up in the Rheumatology Department of our hospital. All patients, who met the criteria of the American College of Rheumatology for RA, had a disease lenght of less than 6 months prior to diagnosis and were treated with at least one disease-modifying drug. Patient follow up was done every three months and all patients had at least one follow up during 2016. The demographic, clinical and laboratory characteristics of the patients were assessed both in the diagnosis of the disease and at the end of the study.

Results

The analysis revealed statistically significant correlation of positivity to aCCP with positivity to Rheumatoid Factor (RF), to Anti-Nuclear Antibodies (ANA), to male sex, to smoking, to Erythrocyte Sedimentation Rate, and to DAS-28 joint disease. No association was found between the presence of aCCPs with the C-reactive protein and the age of the patients. Analysis showed that RF positivity was the strongest factor for the appearance of positive aCCP, followed by high levels of DAS-28 and smoking.

Conclusion

A male patient with early RA, positive RF, smoker, with high disease activity, is very likely to display a positivity in ACCP

AUTO1-0836
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

SILICONE BREAST IMPLANTS AND THE RISK OF AUTOIMMUNE DISEASES- ANALYSIS OF REAL WORLD DATA

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Background: Previous reports have suggested an association between silicone breast implants (SBIs) and connective tissue disorders. However, several epidemiological studies have produced inconsistent results. The aim of this study was to evaluate the association between SBIs and the most clinically relevant auto-immune diseases (ADs) using a large, population based database.

Methods: In this cross-sectional study, we used the computerized databases of Maccabi Healthcare Services which include up to 20 years of data on 2 million members. Women with SBIs were identified by procedure and diagnosis codes, clinical breast examinations and mammography referrals. ADs were identified using the International Classification of Diseases 9th revision (ICD-9) codes. SBIs free women were matched by age group and socio-economic status in a ratio of 1:4. Multivariate logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI).

Results: We included 24,651 SBI recipients and 98,604 matched SBIs free women in our study. The association between SBIs and AD was significant ($p < 0.05$) (adjusted OR 1.21, 95% CI 1.17-1.26). The strongest association with SBIs ($OR > 1.5$, $p < 0.001$) was recorded for systemic sclerosis (SSc) and sarcoidosis (OR of 1.99 and 1.67, respectively). Similar results were calculated when analysis was limited to cancer free women. Multivariate Cox regression model yielded a HR of 1.45 (95% CI 1.21-1.73) for being diagnosed with at least 1 AD in women with SBI compared to those without.

Conclusion: SBIs seems to be associated with higher likelihood of auto-immune disease diagnosis.

AUTO1-0273
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

SAFETY AND EFFICACY OF A TRIVALENT, INACTIVATED INFLUENZA VACCINE IN PATIENTS WITH RHEUMATIC DISEASES (PRELIMINARY RESULTS).

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Background

In rheumatology, infections have significant impact on patients' morbidity, mortality and quality of life. Prevention of infections is an integral part of supervision of these patients. The aim of this study was to evaluate the safety and efficacy of influenza vaccination in patients with rheumatic diseases (RD).

Method

The study included 70 people (women - 49, men - 21, age 22-76 years): 20 patients with rheumatoid arthritis (RA), 13 with ankylosing spondylitis (AS), 7 with systemic scleroderma, 30 control subjects with a history of acute respiratory viral infection and influenza. 12 patients with RA receive methotrexate, 3 - leflunomide, 4 - TNFα-inhibitors, 1 - abatacept. 6 patients with AS receive NSAIDs, 7 - TNFα-inhibitors. Vaccine "Vaxigrip®", included strains of influenza virus of the 2016/17 epidemic period, at 1 dose was injected subcutaneous continued anti-rheumatic therapy. The follow-up period after vaccination was 6 months.

Results

In 57 cases (81.4%) patients tolerated the vaccine without complications. In 7 cases (10%) pain, swelling and redness of the skin were observed, in 6 cases (8.5%) – low-grade fever. These reactions did not require changes in the treatment scheme and resolved within 24 hours. There were no episodes of exacerbation of RD or the occurrence of new autoimmune disorders. Over the entire period of observation, cases of influenza or influenza-like illness were not observed.

Conclusion

Preliminary results indicate good tolerability and effectiveness of the vaccine "Vaxigrip®" in patients with RD. For a more complete assessment of the effecacy and safety of vaccine, further clinical studies are recommended.

AUTO1-0529
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

COMPLEX CASE OF AUTOINMUNE COMPLICATIONS WITH UNUSUAL POSITIVE RESPONSE AFTER AMALGAM REMOVAL

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Background

Autoimmune (Auto-inflammatory) syndrome induced by adjuvants (ASIA Syndrome) is an immune-mediated condition following exposure to a external stimuli. Adjuvants include environment compounds that have been recognized for decades as autoimmunity inducers in different animal models. The syndrome incorporates immune-mediated conditions, all associated with previous exposure to various agents such as vaccines, silicone implants and several others and includes diseases like gulf war syndrome and macrophagic myofascitis.

Method

Here we describe the case of a 48-year-old woman. She had a complex medical history of nickel sulphate contact dermatitis, type II DM, primary biliary cirrhosis, intestinal inflammatory disease. Complaints included polyarthralgias, myalgias, muscular weakness, asthenia, polyadenopathy and chronic kidney disease.

Results

Positive dermal patch for nickel sulphate, palladium chloride, titanium oxide, antimony chloride and amalgam were detected. HLA phenotype: HLA-B 27, DRB1*01, DRB1*07/DQB1*02, DQB1*05. Brain MRI was normal, without demyelinating lesions. The patient removed the amalgam and during a 6 month follow-up a progressive improvement of distinct of the chronic symptoms was observed. After removal of amalgam dermal patch became negative. A MELISA test was performed. HLA phenotype susceptibility, clinical criteria and improvement after amalgam removal might support the diagnosis of ASIA ex juvantibus, in addition to the other clinical complications she had.

Conclusion

ASIA syndrome is part of the differential diagnosis in cases in which a correlation of the exposure to various adjuvants and substances with diverse autoimmune diseases is documented. The potential role of amalgam is suggested.

AUTO1-0475
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

IMMUNOLOGICAL AND ENDOCRINE STATUS OF ESTHETIC SURGERY CLIENTS VERSUS PROSTHETIZED ONCOLOGICAL PATIENTS BEFORE AND AFTER SILICONE BREAST IMPLANTATION

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Background

The silicone has long been suspected as a provoking agent for ASIA due to its possible adjuvant-like role. Precise mechanisms of pathogenetic involvement of silicone grafts into autoimmune disorders are still unclear.

Method

The evaluation of the immunological and endocrine status in 50 persons with the use of silicone grafts, including those with documented adjuvant-related auto-inflammatory reactions, autoimmune diseases and allergic diseases in anamnesis was carried out. The levels of marker autoantibodies of major non-organe specific and thyroid autoimmune diseases, including autoantibodies to thyroglobulin, thyroid peroxidase, TSH receptor, collagen and proteoglycans; endocrine status assessment (T3, T4, thyroglobulin, TSH, prolactin, cortisol, sex hormones), as well as vitamin D levels in blood of esthetic surgery or oncological prosthetized patients before and after silicone breast implantation were studied by ELISA method. Tissue samples before and in various terms after implantation were taken and subdued to pathohistological and immunohistochemical study.

Results

The possible effects of silicone breast implants on the system of prolactin regulation, on status and spectrum of autoimmunity were analyzed comparatively in patients performed silicone breast implantation after breast tumor removal or in healthy persons performed grafting due to esthetic reasons. Morphological characteristic of the tissue samples before and after grafting were followed. The possible mechanisms of silicone grafting influence on autoimmunity and the criteria of predicting autoimmune reactions in patients after silicone breast implantation are discussed.

Conclusion

There are evidences that not only adjuvant-like properties of silicone, but also alteration of prolactin regulation after grafting is of some essence for status of autoimmunity.

AUTO1-0276
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

POST SNAKE BITE PANHYPOPITUITARISM - AN AUTOIMMUNE ENTITY

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Background

Post snake bite panhypopituitarism is a described entity. Most of the cases are diagnosed long after the snake bite. We present 9 cases of post snakebite hypopituitarism, which were diagnosed late, with delayed onset of symptoms.Aim was to study the clinical profile of post snake bite panhypopituitarism & sequence of onset of symptoms, and presentation.

Method

9 patients, who were diagnosed to have post snake bite hypopituitarism between May 2014 and April 2017 were studied.The type of snake, complications & treatment given were studied & time of onset of symptoms of hormonal deficiencies was collected with relevant hormonal tests.

Results

All patients were male, all were bitten by Russels viper, all had hypotension after the bite and required blood transfusions and hemodialysis. The mean duration from the snake bite to the diagnosis was 7.75 years. The onset of symptoms were also delayed, with symptoms occurring an average 4.25 years after the snake bite. All patients had symptoms of hypogonadism, Adrenal crisis and panhypopituitarism. MRI done showed empty sella in 8 patients and small anterior pituitary in 1 patient.

Conclusion

Contrary to our earlier understanding of post snake bite hypopituitarism,the pituitary damage is not a single time event, but a gradual loss of pituitary function initiated by the snake bite, which results in a delayed appearance of symptoms. The sequence of loss of pituitary hormone functions- Gonadotropin- GH-Thyrotropin-ACTH also points to the same fact. The late presentation may be due to an autoimmune destruction of pituitary, initiated by the snake bite.

AUTO1-0336
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

AHR ACTIVATION IN THYMIC EPITHELIAL CELLS CAN MODIFY IMMUNE TOLERANCE PROCESS.

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Background

Environmental contaminants (ECs) are associated with pathogenesis and etiology of numerous chronic diseases. The aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor is the intracellular mediator of the EC effects (Busbee et al., 2013). Various studies have shown that AhR activation induces T-cell disequilibrium that could lead to autoimmunity.

Method

We aimed to study the impact of AhR activation in medullary thymic epithelial cells (mTECs) that are essential for central tolerance mechanisms and T-cell differentiation. To this end, we used primary cultured human TECs that are highly enriched in mTECs.

Results

To this end, we used primary cultured human TECs that are highly enriched in mTECs. We labeled cells with CFSE, and observed that AhR activation enhanced TEC proliferation compared to untreated control cells. In addition, activated AhR induced deregulation of Aire, Fezf2 and Prdm1 mRNA expression, three main transcription factors involved in the immune tolerance mechanisms. A similar effect was found on the expression of several tissue-specific antigens whose expression is dependent on Aire, Fezf2 or Prdm1. More, we observed that AhR modulated cytokine production with an up-regulation of IL-6 and a down-regulation of the anti-inflammatory cytokine, TGF-β, at the mRNA and protein level.

Conclusion

Altogether, these results suggest that AhR activation in mTECs affected cell proliferation, TSA expression and cytokine secretion. These effects could alter the negative selection process (permitting the escape of autoreactive T cells) and the balance of T cells subpopulation. Therefore, EC activation of the AhR pathway could favor the development of autoimmune disorders in predisposed subjects.

AUTO1-0028
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

DECIPHERING THE ROLE OF OXIDATIVE STRESS IN SYSTEMIC LUPUS ERYTHEMATOSUS: IMPLICATIONS IN THE PATHOGENESIS OF DISEASE

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Background

SLE is a systemic autoimmune disease with unknown etiology, increased oxidative stress results from disparity between products of oxidation and antioxidant defenses. Therefore, in the present study we examined the involvement of oxidative and antioxidative parameters in patients with Systemic Lupus Erythematosus (SLE) and also evaluated its correlation with the disease severity.

Method

Oxidative stress was determined by measuring the levels of Lipid Peroxides (LPO), nitric oxide (NO) and Protein carbonyl in plasma and antioxidative parameters like catalase, Glutathione peroxidase (GPx) and Glutathione Reductase (GR) in lysate in 80 patients and 80 healthy controls without SLE. Clinical parameters of SLE were also evaluated.

Results

Concentrations of catalase ($p<0.01$), GR ($p<0.01$) and GPx ($p<0.01$) were significantly lower in SLE patients than in controls, and levels of oxidative stress parameters, LPO ($p<0.01$), NO ($p<0.01$) and Protein carbonyl ($p<0.01$) were significantly higher in patients than in controls. A significant positive correlation was found between LPO and clinical symptoms of SLE among patients group. Furthermore, a significant positive correlation was also found between Protein carbonyl and clinical symptoms of SLE among patients group than in control group.

Conclusion

Present study indicate that SLE patients are exposed to oxidative stress and this escalated oxidative stress may play a role in the etiopathogenesis of the disease. Moreover, our results also show that increased oxidative stress parameters are more strongly amalgamated with SLE symptoms. Furthermore, supplementation of the regular treatment with antioxidants may lead to development of new therapeutic strategies for prevention and treatment of this disease.

AUTO1-0849
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

MMRV VACCINE ASSOCIATED TRANSIENT NEUTROPENIA: DESCRIPTION OF TWO CASES

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Background

Post-vaccination neutropenia is not uncommon. The risk of thrombocytopenia following MMR vaccination is 1 in 30,000 to 1 in 40,000 vaccinated children. The clinical course of these cases is usually transient and benign. The vaccine Priorix Tetra (MMRV) is a vaccine consisting of alive but attenuated measles, rubella, mumps, and varicella-zoster viruses, administrated in two doses: at age of 13-15 months, and 4-6 years.

Method

Cases report.

Results

The first case refers to a 17 months old male child. On the 13th day following the vaccine administration, mild neutropenia was presented (absolute count 970 neutrophils). There were neither IgG, nor IgM anti-Rubella. The second case refers to an 18 months old male child. He showed thrombocytopenia and neutropenia, on the 8th and 9th day after the vaccine injection. Furthermore, on the 32th day following the vaccination, thrombocytopenia showed up once again. IgG anti-parotitis were absent.

Table 1: Laboratory Examinations, Case 2.

Date: year 2017		August 24, 2017: MMRV vaccine injection		
Days after vaccination		White Blood Cells	Neutrophils	Platelets
6th	August 30	6,600	1,500	133,000
8th	September 1	3,650	820	98,000
9th	September 2	5,010	750	124,000
10th	September 3	7,180	1,020	167,000
13th	September 6	6,050	1,150	238,000
32th	September 25	9,130	2,240	46,000
36th	September 29	8,480	2,240	310,000

Conclusion

In this study there are two children who developed a transient neutropenia related to Priorix Tetra vaccine injection. The one of them, also had symptoms very similar to a wild type of measles virus infection, and thombocytopenia. The possibility of hematologic adverse events following MMRV vaccination is real, and not always the vaccinated child is immunized against all the viruses present in this vaccine. This partial immunization, if presented throughout the population, suggests that immunity control is more important than the mere number of injected vaccine doses.

AUTO1-0755
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

Reasons Why Patients Failed Vaccinations Vs Influenza and Pneumococcus. Monocentric Cross-Sectional Study

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Background

According to the EULAR guidelines, all patients affected by autoimmune/inflammatory diseases should receive vaccinations against influenza and pneumococcus. The primary aim of this work is to evaluate the prevalence of flu and pneumococcal vaccinations in a cohort of patients affected by inflammatory arthritides and SLE treated with biological drugs.

Method

We administered a self-reporting questionnaire about both flu and pneumococcal vaccination, to 274 consecutive patients in 2017 treated with bDMARDs.

Results

65.3% of patients declared to have been informed from rheumatologist about the possibility to received vaccinations during biological treatments but the 19.5% declared to have never been informed about them. The 46% of patients vaccination for influenza was performed after rheumatology suggestion and the 21%after their general pratictioner suggestion, while the 30.1%has declared to have not performed it for several reasons. The anti pneumococcal vaccination was administered to the 25.3%, while to the 50.3%has never been suggested to do it. The 97.3% would have undergone vaccination even for a fee. At last the patients have declared to have always been well informed about vaccinations (48,9%), to have been well informed only about certain vaccinations

(9,5%) or to have been informed only after asking (9,1%);(fig 1).

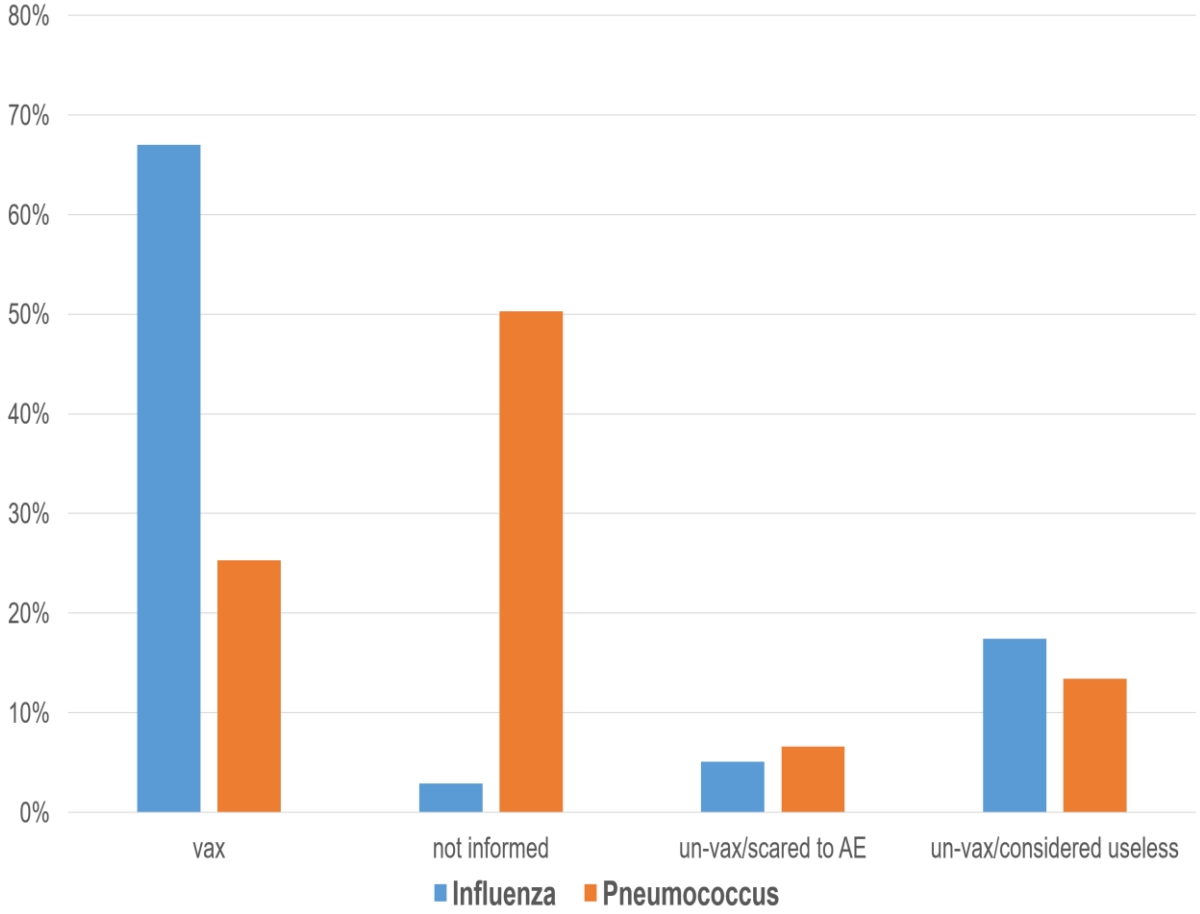

Figure 1: vaccination rate.

Conclusion

The acquired vaccine rate has been low for the influenza vaccination (<60%) and extremely low for the pneumococcal vaccination (26%). Even if the reasons of this results are partially attributable to a low patients' compliance, almost 20% has declared not to have ever been informed about vaccinations. An Additional effort to improve these results is mandatory.

AUTO1-0096
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

SMOKING HABITS INCREASE THERAPEUTIC FAILURES OF BIOLOGICS, SPECIFICALLY TNF-INHIBITORS IN RHEUMATOID ARTHRITIS: A POSSIBLE CROSS-TALK BETWEEN TNFa AND SMOKING (AhR) SIGNALINGS.

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Background

Previously, we analyzed the causes of discontinuation of biologics (Bio)-use using the data from the “NinJa” Registry, one of the largest cohorts of Japanese RA patients (11,940 patients) and reported the discontinuation caused by therapeutic failure, “Failure” was significantly associated with smoking habits. In this study, we examined the association between “Failure” and smoking habits among the different Biologics individually.

Method

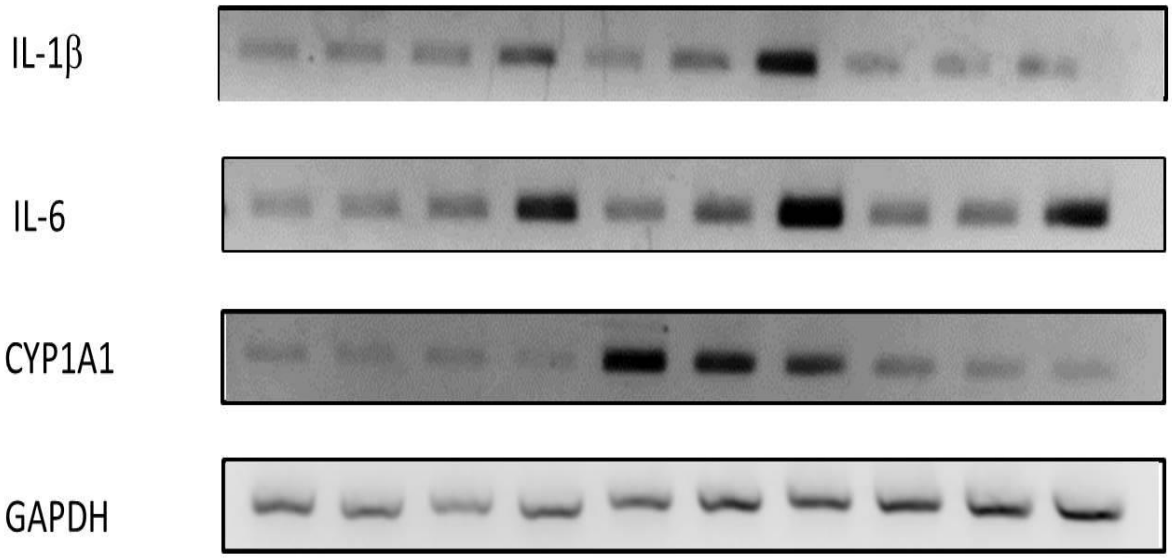
Smoking habit was assessed by a questionnaire and the patients were divided into three groups, current-smoking(C), non-smoking (N), and ever-smoking (E).The association between the discontinuation caused by “Failure” and smoking habits was analyzed statistically (OR:odds ratio). *In-vitro production of* inflammatory cytokines such as IL-6 and IL-1 were measured by ELISA and RT-PCR.

Results

“Failure” in both in (N) and (E) was significantly less frequent compared to (C) (OR:(N)/(C) 0.678, 95% CI [0.482, 0.967], p=0.032; (E)/(C) 0.557, 95%CI [0.357, 0.869], p=0.010) and the influence of smoking was more particular in TNF inhibitors (TNFi)

/Current Smoking (C)	TNF inhibitors (IFX, ETN, ADA,,GLM)	IL-6 inhibitor (TCZ)	T cell inhibitor (ABT)
Non-smoking (N)	OR=0.672, 95%CI [0.457,1.003], p=0.052	OR=1.035, 95%CI [0.331, 4.562], p=0.9576	OR=0.773, 95%CI [0.241, 2.982], p=0.686
Ever-smoking (E)	OR=0.584, 95%CI [0.355, 0.958], p=0.033*	OR=0.315, 95%CI [0.040, 2.10], p=0.216	OR=0.729, 95%CI [0.165, 3.370], p=0.675

In addition, a cigarette chemical constituent, benzo[a]pyren (BP) significantly enhanced the production of both IL-6 and IL-1 at both protein and mRNA levels in the presence of TNFa stimulation using an immortalized rheumatoid synovial cell line, MH7A. A CYP1A2 inhibitor, a-Naphthoflavone (a-NP) as an antagonist for AhR signaling diminished the enhancement of cytokine production completely



TNFα(ng/ml)	-	0.1	1	10	0.1	1	10	0.1	1	10
BP (5μM)	-	-	-	-	+	+	+	+	+	+
α-NP (5μM)	-	-	-	-	-	-	-	+	+	+

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Conclusion

These results suggest that smoking habits decrease the responsiveness of Bio(s) in RA, especially in the case of TNFi. In addition, a cross-talk between TNFa and smoking (AhR) signalings is suggested as a possible molecular mechanism.

AUTO1-0857
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

STROKE POST INFLUENZA VACCINATION: A POSSIBLE ASSOCIATION.

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Background

Influenza epidemic have been shown to increase the levels of vascular events including stroke . Several reports have demonstrated a link between the influenza vaccination and a reduction in stroke risk. In this article, we report a 62 years old female patient with no classical risk factors for adverse vascular events. She developed a hemorrhagic stroke five weeks post-vaccination from the influenza vaccination. Vaccination encompasses viral antigen and an adjuvant which can provoke a severe inflammatory response in susceptible individuals. Common mechanisms of this reaction include molecular mimicry, polyclonal activation and the bystander effect. Although this vaccination is known to reduce the risk of stroke in the general population, it is important to examine if a neurologic disease (i.e. stroke) may occur post-vaccination in certain genetically susceptible individuals. The awareness of physicians is warranted in assessment of post-vaccination complications. This is especially true in the cases of long latencies between vaccination and adverse event which would otherwise be overlooked.

Method

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Results

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Conclusion

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AUTO1-0129
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

INFLAMMATION AND ACCUMULATION OF ADIPOSE TISSUE MACROPHAGES IN MICE EXPOSED TO LOW DOSE BISPHENOL A

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Background

Adipose tissue low-grade inflammation characterized by macrophages infiltration is a key pathogenesis linking the global epidemic of obesity. Bisphenol A (BPA), an environmental endocrine disruptors, has been identified as obesogens that contribute to promoting obesity. However, whether BPA promotes macrophage accumulation in adipose tissue and mediates inflammatory is still not clear.

Method

The C57BL/6J mice fed normal diet (ND) or high-fat diet (HFD) were exposed to BPA (10, 100 or 1000 nM) via drinking water. At 8, 12, 16 and 20 weeks, inflammation and inflammatory mediators expression in adipose tissue were evaluated using histology and immunohistochemistry, ATMs accumulation was analyzed by F4/80 expression, ATMs activation was detected by number of M1 and M2 populations, mRNA expression of CD11c and CD206, cytokine secreted by M1 and M2 ATMs, respectively.

Results

BPA induced more weight gain in HFD feeding than did the ND feeding mice. Adipocytes enlargement, adipose tissue infiltrated with inflammatory cells, IL-6 and IL-1βexpression were elevated in BPA dose and time-dependent manner from ND or HFD feeding mice. Infiltration of F4/80 macrophages into adipose tissue was increased in BPA exposed mice fed with ND or HFD. Proinflammatory M1 ATMs number, CD11c expression and M1 ATMs secreting cytokine were enhanced in BPA dose and time-dependent manner from ND or HFD feeding mice, while M2 ATMs number, CD206 expression and M2 ATMs secreting cytokine are not shown the same trends.

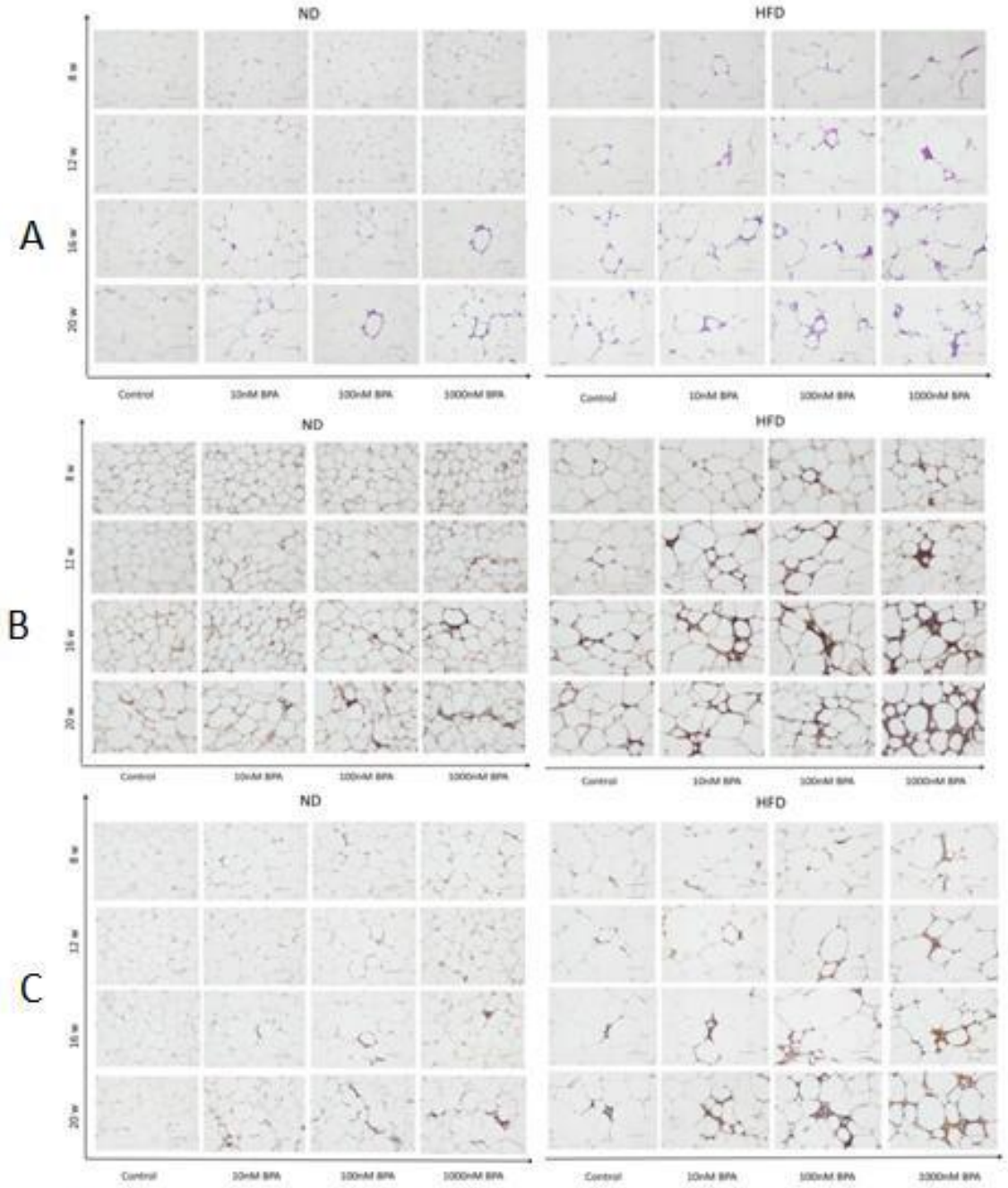

Fig.1 BPA aggravates inflammation of adipose tissue. (A) H&E staining from epididymis fat tissue; (B and C) Representative immunohistochemistry images of IL-6 (B) and IL-1β (C) expression (brown) in epididymal adipose tissue. Scale bars, 400μm.

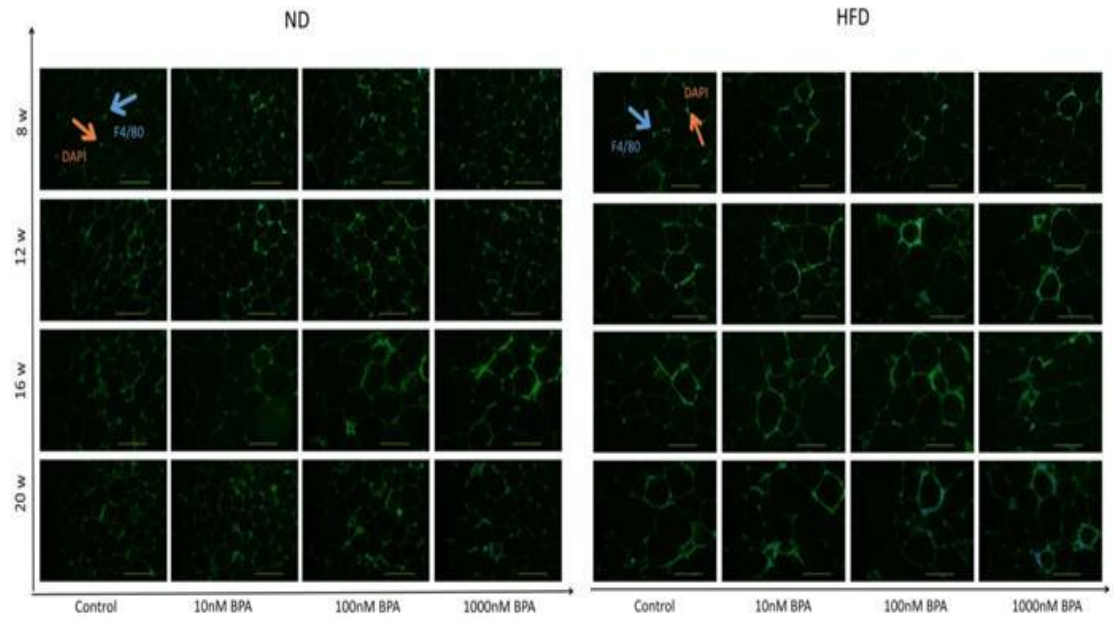

Fig.2 BPA increases accumulation of ATMs in adipose tissue. Immunofluorescence staining for F4/80 (blue) and DAPI (green) in epididymal adipose tissue. Scale bars, 400μm.

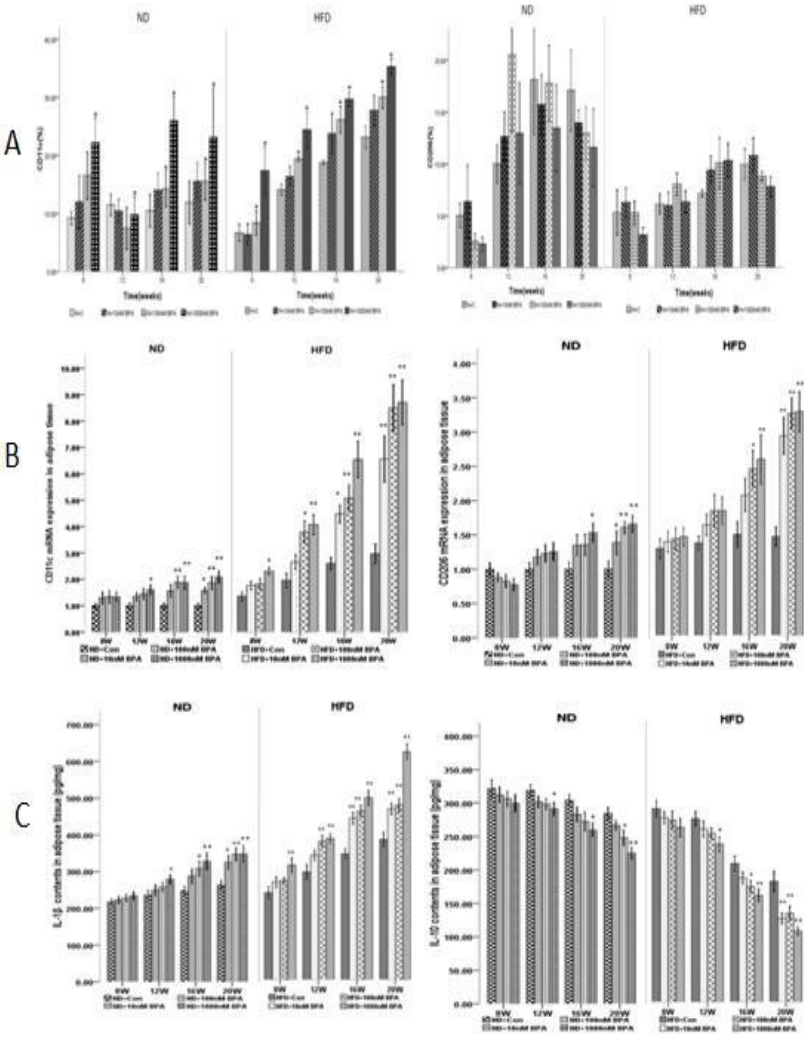

Fig.3 ATMs activation in epididymal stromal vascular fractions from BPA exposed mice. (A) Flow cytometry analyses the number of $F4/80^{+}CD11c^{+}CD206^{-}$(M1 ATMs) and $F4/80^{+}CD11c^{-}CD206^{+}$(M2 ATMs). (B) Real-time quantitative polymerase chain reaction (RT-qPCR) measures mRNA expression of the indicated M1 marker genes (CD11c) and M2 marker genes (CD206). (C) Enzyme-linked immunosorbent assay (ELISA) quantifies content of cytokines secreted by M1 ATMs(IL-1β) and M2 ATMs(IL-10). Data expression as mean ± SEM(n = 6 mice).

Conclusion These findings indicated that BPA may promote proinflammatory ATMs accumulation in adipose tissue and mediate inflammatory during obesity induced by BPA.

AUTO1-0585
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

THE FIRST CASE OF BACILLUS CALMETTE-GUERIN INDUCED SMALL-VESSELCENTRAL NERVOUS SYSTEM VASCULITIS

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Background

To present an unrecognized vascular complication of Bacillus Calmette-Guérin (BCG) therapy administered for superficial bladder carcinoma. We also briefly review the potential mimickers for primary angiitis of the central nervous system (PACNS) as well as complications of intravesical BCG therapy.

Method

A 89 year old Caucasian man with a history of relapsing high-grade bladder carcinoma treated 5 years earlier with intravesical BCG presented with recurring episodes of right upper limb paresthesia with clumsiness, and dysarthria.

Results

Magnetic resonance imaging of the head revealed multiple predominantly left-sided frontotemporal micronodular peri-vascular lesions. Left frontal lobe biopsy showed non-necrotizing granulomatous vasculitis. Urine and vitreous cultures were positive for mycobacteria, later identified as Mycobacterium bovis. Brain biopsy was reviewed with Auramine and Fite-Faraco staining which demonstrated the presence of mycobacteria. A retrospective diagnosis of BCG-induced central nervous system vasculitis was made. The patient was treated with high-dose corticosteroids, moxifloxacin, isoniazid, ethambutol, and rifampicin.

Conclusion

BCG is a live attenuated form of Mycobacterium bovis widely used as tuberculosis vaccination and intravesical therapy for superficial forms of bladder cancer. Cases of endophtalmitis, meningitis, aortitis or mycotic aneurysms have been described, but no reports of CNS vasculitis have been found. Systemic infections are usually present within weeks but can manifest months or years after the last instillation.
This is the first documented case of BCG-induced small-vessel CNS vasculitis. Mycobacterium bovis infection is rare and findings are often nonspecific, making the diagnosis very difficult. Other infectious and non-infectious causes must be ruled-out appropriately before considering this entity.

AUTO1-1014
ENVIRONMENT, VACCINATION, ADJUVANTS (ASIA SYNDROME), AND AUTOIMMUNITY

CHANGES OF THE STRUCTURE OF SEMINAL VESICLES OF REPRODUCTIVE AGE RATS IN CONDITIONS OF CYCLOPHOSPHAMIDE-INDUCED IMMUNOSUPRESSION

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Background

In recent decades, the number of autoimmune conditions that require comprehensive and full-fledged drug treatment is steadily increasing. Cyclophosphamide is a drug that has long been widely used to achieve an immunosuppressive state. The development of autoimmune diseases affects not only the target organs, but also the entire body as a whole, including the reproductive system.

Method

The immunosuppressive state was modeled on 60 white rats of reproductive age by administration of cyclophosphamide at a dosage of 1.5 mg/kg body weight intramuscularly tenfold. The organs were weighed on a torsion balance, the relative mass was calculated, the length, width and thickness were determined by means of a caliper. The volume of the organ was established by the method of displacement of water in a graduated cylinder containing distilled water.At the microscopic level, the organs examined the height and width of epithelial cells, their volume, and also the larger and smaller diameters and the volume of the cell nuclei.

Results

A statistically significant decrease in all the studied parameters occurred after 7, 15 and 30 days. The deviation of the value of the length indicator was 13.55%, 16.05% and 14.62%, respectively. The width and thickness of seminal vesicles decreased on 5.62%, 4.77%, 3.16% and 10.78%, 12.25%, 4.82%. Decrease in body volume were 27.16%, 29.86%, 21.30%, in the height and width of the epithelium was 4.61%, 5.02%, 7.09% and 4.87%, 6.64%, 7.91%. The size of the nuclei, their volume decreased at the same time.

Conclusion

Seminal vesicles undergo pronounced changes in response to long-term immunosuppression.

AUTO1-0439
EXPERIMENTAL AUTOIMMUNE MODELS

HYPOSALIVATION AND ITS POSSIBLE TREATMENT IN DIFFERENT EXPERIMENTAL AUTOIMMUNE MODELS

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Background

The prevalence of xerostomia is higher in autoimmune disorders including Sjogren's syndrome and aging. Type 1 diabetes and aging, an autoimmune diseases contributes to dry mouth syndrome. Non-obese diabetes and aging animal models have been used to correlate the secretory dysfunction of the salivary glands.

Method

Streptozotocin (65 mg/kg, ip)-induced type 1 diabetic rats and aging (22 months old) associated dry mouth was used in our study. The ethanol extract of *Ixeris dentata* (IXD, Korean herbal medicine) 100 mg/kg (for diabetic rats/10 days treatment) and 25, 50 and 100 mg/kg (for aging rats/8 weeks treatment) was used to increase salivation. Pilocarpine (0.6 mg/kg) was injected to stimulate saliva and pre-weighted cotton balls were used to collect saliva. After collection, submandibular gland was excised and stored in 3.7% formalin and at -80 ºC for further analysis.

Results

In our study, we found that diabetes and aging rats induced salivary dysfunction. Alteration of submandibular gland weight and the salivary flow was found in both diabetes and aging rats. The salivary alpha-amylase expression was less in both diabetic and aging submandibular gland as well as in saliva. The water channel protein Aquaporin-5 and Sodium-hydrogen exchanger-1 were downregulated in submandibular gland tissue. Treatment with IXD extract upregulated the AQP5 and also improved the salivary function. Moreover, the IXD extract improved the protein folding capacity of the endoplasmic reticulum (ER) and also regulated the ER stress response associated with salivary gland dysfunction.

Conclusion

IXD extract regulates salivary function through the regulation of ER stress in a hyposalivation-animal model.

AUTO1-0343
EXPERIMENTAL AUTOIMMUNE MODELS

MULTIFACTORIAL NATURE OF AUTOIMMUNE DISEASE: LESSONS LEARNED FROM THE SMYTH CHICKEN MODEL FOR AUTOIMMUNE VITILIGO

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Background

Autoimmune vitiligo is a pigmentary disorder characterized by immune system mediated post-natal loss of epidermal melanocytes (pigment cells). The best-established animal model for spontaneously developing autoimmune vitiligo is the Smyth line (SL) of chicken. Over the past 25 years, many parallels between human- and SL-vitiligo have been clearly demonstrated, supporting the importance of this model for basic biomedical research and treatment testing.

Method

The SL-model consists of three MHC-matched lines of chickens: the vitiligo-susceptible SL with a predictably high incidence of vitiligo (80-95% incidence), the parental vitiligo-susceptible Brown line (BL) that rarely expresses the disorder (<2% incidence), and the Light-brown Leghorn chicken which is vitiligo resistant. In SL-vitiligo, the target tissue is the living portion (pulp) of growing feathers (an 8-10 mm by 2 mm column of dermis enveloped by epidermis). This skin derivative is one of the most unique features of this autoimmune disease model, as it provides minimally invasive and repeated access to the target-tissue prior to and throughout vitiligo development.

Results

In vitro and in vivo studies demonstrated the central role of Th1-mediated immunity in melanocyte loss, identified a reliable environmental trigger for SL-vitiligo (routine live herpesvirus vaccination), and revealed aberrant melanocyte-/melanogenesis-related activities during induced cellular stress. Like in human patients, SL-vitiligo may also be associated with other autoimmune disorders, such as autoimmune hypothyroidism, alopecia areata, and uveitis/blindness due to autoimmune attack of choroidal melanocytes.

Conclusion

The Smyth vitiligo model is ideally suited for incorporation as an intermediate model in collaborative biomedical research on mechanisms, treatment, and prevention of autoimmunity.

AUTO1-0590
EXPERIMENTAL AUTOIMMUNE MODELS

THE ROLE OF INTERLEUKIN-22 AND ITS RECEPTOR IN THE DEVELOPMENT AND PATHOGENESIS OF EXPERIMENTAL AUTOIMMUNE UVEITIS.

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Background

Recent studies have reported the increased number of IL-22 producing T cells in patients with autoimmune noninfectious uveitis; however, the correlation between IL-22 and uveitis remains unclear. In this study, we aimed to determine the specific role of IL-22 and its receptor in the pathogenesis of uveitis.

Method

IL-22 concentration in uveitis patients was measure by ELISA and its receptor expression was by RT-PCR. The role of IL-22 and its receptor on the pathogenesis of uveitis was confirmed by the treatment of recombinant IL-22. Their in vivo function was examined by using of animal model after treatment of interphotoreceptor retinoid binding protein 1-20 (IRBP).

Results

IL-22 was significantly increased in uveitis patients. IL-22Rα was expressed in the retinal pigment epithelial cell line, ARPE-19. The proliferation of ARPE-19 was definitely elevated by treatment of rIL-22. In experimental animal models of uveitis, we found hyperplasia RPE and IL-22 production. We found the regulatory role of cysteamine, which has an anti-inflammatory role in the cornea, in uveitis through the down-regulation of IL-22Rα expression.

Conclusion

These finding suggest that IL-22 and its receptor have a crucial role in the development and pathogenesis of uveitis by facilitating inflammatory cell infiltration, and that cysteamine may be a useful therapeutic drug in treating uveitis by down-regulating IL-22Rα expression in RPE.

AUTO1-0624
EXPERIMENTAL AUTOIMMUNE MODELS

DYSBIOME AND THE LEAKY GUT COMBINE AUTOIMMUNITY, INFECTIONS AND ALLERGY: COMMON PATHWAYS

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Background

During the last decades, the incidence of autoimmune diseases and allergic conditions is surging and both are tightly related to microbial components.

Method

Database research to find common pathways relating autoimmunity, allergy and infections and to explore the possibility that gut events are shared between the three.

Results

Several enteric eco-events are suggested to combine autoimmunity, allergy and infectious:

1. Environmental factors contain microbes, allergens, both impacting autoimmunogenesis

2. Various nutrients, nutritional constituents and processed food additives are impacting the microbiota/dysbiota ratio, thus increasing intestinal permeability

3. Enzymatic posttranslational modification of naïve proteins, where dysbiota, associated with autoimmune and allergic conditions, turn them to non-self, immunogenic peptides

4. Multiple allergens, infections and autoimmune environmental factors are breaching tight junction integrity and inducing the leaky gut syndrome

5. The human intestinal ecosystem is newly exposed to transformed microbial transmittable genes that the modern nutritional, bacterial, zoological, food technologies, bio-engineered and synthetic biology is bringing to the gut dynamic environment. By horizontal gene transfer they exchange virulent factors to human eukaryote cells thus merging autoimmunity, allergy to bugs and us.**Conclusion**

Various environmental factors are driving infections, dysbiotic transformation, posttranslational modification of peptides, increased intestinal permeability, leaky gut and detrimental horizontal gene exchange with our self-cells, thus enhancing autoimmunity, allergy and infection triad.

AUTO1-0626
EXPERIMENTAL AUTOIMMUNE MODELS

GLUTEN IMMUNOLOGICAL SIDE EFFECTS ARE DETRIMENTAL TO HUMAN AND NOT ONLY TO GLUTEN SENSITIVE POPULATIONS

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Background

Evolution was accompanied by enrichment of gluten content in the wheat and today 80% of the proteins are gluten. In parallel, some unwanted effects induced by gluten consumption in non-celiac affected populations were recently described.

Method

A systematic review was performed, using Medline, Google, and Cochrane Library databases to summarize the literature for gluten consumption, side effects and withdrawal effects on autoimmune diseases.

Results

The following non-celiac conditions respond partially to gluten-free diet (GFD): Transaminasemia, type 1 diabetes, rheumatoid arthritis, dermatitis herpetiformis, thyroiditis, gluten ataxia and multiple sclerosis. Several pathophysiological avenues were described for the detrimental effects of gluten: breach of intestinal tight junction integrity, decreased viability and apoptosis induction in human cell-lines, induction of neutrophil migration, decrease in NKG2D and ligand expression, increased Th17 population, effects on regulatory T-cell subsets, change in innate immunity and dendritic cell functions, change of Th1/Th2 profile and change in diversity of the microbiome.

Conclusion

Multiple non-celiac autoimmune diseases and conditions respond, to a variable degree, to GFD. The protective mechanisms of GFD are constantly unraveled and involve multiple immunoregulatory pathways. Since transglutaminase 2 is pivotal in posttranslational modification of gluten and autoimmunogenesis, and since the enzyme is active in all organs and cells, GFD might slow its activities and disease progression. Several evolutionary processes and pathophysiological pathways can explain the detrimental health effects of gluten consumption in humans.

AUTO1-0708
EXPERIMENTAL AUTOIMMUNE MODELS

THE FORMATIONS CHANGE OF IMMUNOCYTE CLUSTERS AND SPACE LEARNING DEFECTS IN HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 KNOCKOUT MICE

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Background

Heterogeneous ribonucleoprotein A1 (hnRNP A1) is an important molecule in regulating alternative splicing. Previous studies, we generated hnrnp a1 knockout mice. The knockout mice showed embryonic lethality because of muscle developmental defects.HnRNP A1 promotes the epithelial-type exon usage of CD44, and autoantibodies to hnRNP A1 cause altered 'ribostasis' and neurodegeneration. These suggested hnRNP A1 had critical role in immune.

Method

Although the heterozygous knockout mice did not exhibit an obvious phenotype, we found that they had defects in behavior. These mice were testing during rota-rod testing and the Morris water maze.In immune function, we found that formation of immunocyte clusters in hnrnp a1 defect mice by flow cytometry.

Results

We found that mice had defects in behavior. These mice quickly fell during rota-rod testing and were slow to arrive at the platform in the Morris water maze. These data suggested that the hnRNP A1 heterozygous mice had poor motor coordination, sense of balance, and spatial learning. We found that formation change of immunocyte clusters in hnrnp a1 defect mice, especially in $CD3^+$, $CD3^+CD4^+$. The formations in these cells were significant increase in hnrnp a1 defect mice. These data indicated that help T cell were increase in these mice not cytotoxic T cell. The ratio of $CD4^+CD8^+$ was increase in hnrnp a1 defect mice.

Conclusion

Our data demonstrated that hnRNP A1 plays a critical and irreplaceable role in motor coordination, sense of balance, and spatial learning and regulated in formation of immunocyte clusters. This mouse may be the animal model for studying immunity.

AUTO1-1064
EXPERIMENTAL AUTOIMMUNE MODELS

PARTICIPATION OF ANTIMICROBIAL PEPTIDES / AMPS IN THE PHYSIOPATHOGENESIS OF JOINT DAMAGE MEDIATED BY METALLOPROTEINASES / MMPS IN ARTHRITIS INDUCED BY TYPE II COLLAGEN.

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Background

Antimicrobial peptides (AMPs) are molecules with antimicrobial activity, however, they are also able to modulate different activities of cells. In chronic inflammatory diseases such as rheumatoid arthritis (RA), increased levels of AMPs have been observed. In this study we determined the expression of AMPs, rCRAMP, mBD-3, mBD-4 and MMP-3 during the progression of the collagen induced arthritis (CIA), with the purpose of associating their expression levels with the histopathological changes of the different phases of the CIA

Method

CIA was induced by collagen and complete Freund's adjuvant. Clinical severity was assessed using a scoring system, the joints were classified at onset, peak and remission. After the animals were sacrificed, the joints were dissected and histological sections were prepared, stained with hematoxylin-eosin and safranin O respectively. Detection of the peptides rCRAMP, mBD-3, mBD-4 as well as MMP-3, was carried out by immunohistochemistry.

Results

Cell infiltration was found to be increased in peak and remission phase, as was the degradation of cartilage. MMP-3 expression increased in the peak phase and was localized in infiltrated cells. CRAMP expression is constitutively present and increases in peak and remission phases, in addition, it was associated with cellular infiltration, cartilage degradation and MMP-3 expression. The expression of mBD4, showed a tendency to increase in infiltrated cells and synovial membrane in the peak phase, this showed a positive association with cellular infiltration. mBD3 showed low expression in all phases

Conclusion

The results suggest that the antimicrobial peptide CRAMP is associated with the development and progression of collagen-induced arthritis.

AUTO1-0657
EXPERIMENTAL AUTOIMMUNE MODELS

CALCITRIOL TREATMENT AMELIORATES INFLAMMATION AND BLISTERING IN MOUSE MODELS OF EPIDERMOLYSIS BULLOSA ACQUISITA

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Background

A link between hypovitaminosis D and development of autoimmune bullous disorders has been recently suggested, but this association has not been experimentally elaborated.

Method

Here, the role of vitamin D was investigated in experimental models of epidermolysis bullosa acquisita (EBA), an anti-type VII collagen autoantibody-induced blistering skin disease.

Results

Oral administration of the hormonally active vitamin D metabolite calcitriol ameliorated clinical disease severity and dermal neutrophil infiltration in both an antibody transfer- and immunization-induced EBA mouse model. Mechanistically, calcitriol hindered immune effector cell activation as evidenced by increased L-selectin expression on Gr-1$^+$ cells in calcitriol-treated mice with antibody transfer-induced EBA as well as suppressed in vitro immune complex-induced reactive oxygen species production in calcitriol-treated murine neutrophils. Additionally, calcitriol administration was associated with an increase of regulatory T (CD4$^+$FoxP3$^+$) and B (CD19$^+$IL10$^+$) cells as well as reduction of pro-inflammatory Th17 (CD4$^+$IL-17$^+$) cells in mice with immunization-induced EBA. In line, levels of circulating anti-type VII collagen autoantibodies were lower in mice that received calcitriol compared to solvent-treated animals.

Conclusion

Together with the observed state of hypovitaminosis D in most cases of an analyzed EBA patient cohort, the results of this study support the use of vitamin D derivatives or analogs for patients with EBA and related diseases.

AUTO1-0934
EXPERIMENTAL AUTOIMMUNE MODELS

CD40-CD40L PATHWAY ACTIVATION IN TERTIARY LYMPHOID ORGANS CONTRIBUTES TO DISEASE PATHOLOGY IN PRIMARY SJOEGREN'S SYNDROME

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Background

T cell-dependent activation of B lymphocytes in germinal centers (GCS) within secondary lymphoid organs results in long-lived protective antibody responses. In autoimmune diseases, GC-like structures are found in other tissues, including the salivary glands of primary Sjoegren's syndrome (pSS) patients. Non-obese diabetic (NOD) mice spontaneously develop sialadenitis resembling pSS in humans, providing a model for this autoimmune disease.

Method

We investigated CD40 and CD40L expression by immunostaining in minor salivary glands and CD40 signature in parotid glands from pSS patients. Furthermore, the effects of CD40-CD40L blockade on tertiary lymphoid organs (TLOs) formation, autoantibodies production and function of the salivary glands were investigated in NOD mice treated with MR1 (anti-CD40L) antibody.

Results

Immunohistochemistry revealed CD40 and CD40L expression on B and T cells within the TLOs in minor salivary glands in pSS patients, and upregulation of a portion of the B cell CD40 gene signature, suggesting CD40 pathway activation in lymphocytes within disease-relevant tissue. Wild-type NOD mice developed sialadenitis, TLOs in salivary glands and circulating anti-SSA autoantibodies. in contrast, none of these findings were observed in CD40-deficient NOD mice. Anti-CD40L treatment resulted in disaggregation in splenic GCs as well as established TLOs in NOD mice and decreased levels of IgG secreting cells in salivary glands.

Conclusion

Our data indicate that CD40 pathway is essential for formation and maintenance of salivary gland TLOs and is involved in establishing TLOs from pSS patients, supporting the notion that blockade of CD40-CD40L interactions may provide therapeutic benefit in these patients.

AUTO1-0446
GASTRO INTESTINAL AUTOIMMUNITY

PRIMARY BILIARY CHOLANGITIS-AUTOIMMUNE HEPATITIS OVERLAP SYNDROME – A CASE REPORT

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Background

INTRODUCTION: Primary biliary cholangitis (PBC) and Autoimmune hepatitis (AIH) are two distint autoimmune liver diseases with specific clinical, laboratory and histological criteria. Some patients present with overlapping features of this disorders, and for so are classified as having a “overlap syndrome”.

Method

Results

CASE DESCRIPTION: A 24-year-old healthy male presented in the emergency room with a 1-week-old history of astenia, headache, fever and abdominal pain. On examination, a maculopapular exanthema was revealed. The patient denied regular alcohol consumption or other possible hepatotoxic substances. He had dimished blood counts of leukocytes (3620/uL) and platelets (38000/uL), serum transaminases elevated in 5-fold the normal value, elevated serum alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) levels in 3-fold the normal value and unconjugated hyperbilirubinemia. Laboratory assays also showed prolonged prothrombin time test. The abdominal ultrasound revealed a heterogeneous and granular liver, portal vein ectasia and a large homogeneous splenomegaly. The diagnosis of hepatitis A, B, C and HIV were excluded. The Epstein-Barr virus serology was inconclusive (positive IgG but IgM in the doubtful range). A autoimmune screen was perfomed and revealed positive serum antinuclear antibodies, anti-smooth muscle antibody and antimitochondrial antibody. The liver biopsy ackownledged chronic hepatitis in the cirrhosis state and evidence of interface hepatitis. Therefore this patient meets the diagnostic criteria for overlap syndrome of PBC and AIH.

Conclusion

CONCLUSION: The authors present this clinical report because it highlights the diagnostic dificulties that this rare conditions had set to us. In front of a situation with so inespecific presentation, a thorough workup is mandatory.

AUTO1-0765
GASTRO INTESTINAL AUTOIMMUNITY

CLINICAL PERFORMANCE EVALUATION OF QUANTA FLASH CALPROTECTIN

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Background

Fecal calprotectin is an important biomarker as an aid in the diagnosis of inflammatory bowel disease (IBD) and especially in the differentiation of IBD from irritable bowel syndrome (IBS). This study aimed to assess the clinical performance of the novel chemiluminescent immunoassay (CIA), QUANTA Flash Calprotectin.

Method

The study included 124 stool samples from patients with IBD (n=38) and IBS (n=43) along with relevant controls (n=43). All samples were tested by CIA (QUANTA Flash Calprotectin, Inova Diagnostics, San Diego, USA), by a fluorescence immunoassays (FEIA) (EliA Calprotectin, first generation, Thermo Fisher) as well as by ELISA (QUANTA Lite Calprotectin Extended Range, Inova Diagnostics, San Diego, USA).

Results

Similar clinical performance was found for the new CIA and other two methods using ROC analysis (area under the curve (AUC) 0.886 for QUANTA Flash Calprotectin, 0.886 for Thermo Fisher EliA Calprotectin, 0.884 for QUANTA Lite Calprotectin Extended Range). Additionally, excellent agreement was found between all assays [total percent agreement (TPA) 90.3%, *kappa* 0.81 for CIA vs. FEIA, TPA 91.9%, kappa 0.84 for CIA vs. ELISA and TPA 88.7%, kappa 0.78 for FEIA vs. ELISA) on the entire cohort using a cutoff of 50 mg of calprotectin per kg of stool.

Conclusion

QUANTA Flash Calprotectin CIA demonstrated excellent clinical performance in this cohort of IBD patients, IBS patients and controls and also showed a high level of agreement to the other two traditional ELISA methods.

AUTO1-0088
GASTRO INTESTINAL AUTOIMMUNITY

THE EFFECTIVENESS OF TREATMENT OF PATIENTS WITH LUMINAL A FORM OF CROHN'S DISEASE MESENCHYMAL STROMAL CELLS BONE MARROW 7 YEARS OF FOLLOW-UP

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Background

To examine the long-term efficacy (7 years) therapy mesenchymal stromal cells (MSCs) from the bone marrow of patients with luminal Crohn's disease (CD).

Method

80 patients with CD were divided into two groups. The first group(n=34) received the culture of MSCs . The second group of patients with CD (n=46) received therapy with glucocorticosteroids (GCS) and immunosuppressive (IS). Evaluation of the effectiveness of therapy on the level of the index of activity of Crohn's disease (CDAI).

Results

In 1-st group relapse in the 12 months of observation occurred in 4/36 patients (11.76%). In 2-st group, relapse occurred in 5/46 (10.8%) (p=0.82). After 24 months in the 1-st group of patients receiving MSC, relapse occurred in 6/34 (17.6%). In the 2-nd group of patients relapse in 19/27 (41.3%) (p=0.044). After 36 months in 1-st group patients with a relapse of the disease in 11/34 (32.3%). In the 2-nd group relapse 29/46 (63.1%) (p=0.01). After 48 months in 1-st group, receiving MSCs, relapsed in 15/34 (44.1%). In the 2-nd group relapse in 33/46 (71.7%) (p=0.023). After 60 months in the 1-st group relapse in 19/34 (55.9%). In the 2-nd group relapse 40/46 (86.9%) (p=0.004). After 72 months in 1-st group relapse 25/34 (73.5%). In 2-nd group relapse of the CD in 45/46 (97.8%) (p=0.001). After 84 months in 1-st group relapse CD in 29/34 (85.3%). In the 2-nd group relapse occurred in 46/46 (100.0%) (p=0.011).

Conclusion

MSCs transplantation helps to maintain a long-term clinical remission in patients with Crohn's disease compared with GCS/IS therapy.

AUTO1-0089
GASTRO INTESTINAL AUTOIMMUNITY

DYNAMICS OF CYTOKINES IN THE MUCOSA OF THE COLON AFTER TRANSPLANTATION OF MESENCHYMAL STROMAL CELLS OF BONE MARROW.

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Background

Objective: to determine changes in the level of Pro - and anti-inflammatory cytokines in the mucosa of the colon after transplantation of MSCs, infliximab (IFX) and systemic glucocorticosteroids (GCS).

Method

96 patients with UC . The first group (n=36) received the culture MSCs of 2 million/kg. The second group (n=30) received the IFX. The third group (n=30) received corticosteroids. Biopsies were taken before and 2 months after treatment. In extracts we determined the content of TNF-α, INF - γ, IL-4.

Results

After 2 months the 1-st group TNF-α decreased with 358,67±38,1 pg/g tissue to 187,67±18,9 pg/g tissue, INF-γ - 1207,6±125,3 pg/g tissue - to 499,2±50,2 pg/g tissue ($p<0.05$); the level of IL-4 - 541,6±43.7 to 312±29,8 pg/g tissue ($p<0.05$). In the 2-nd group after the therapy the levels of TNF-α fell to the 122.7±10,7 pg/g tissue, the level of INF-γ decreased to 534,5±48,9 pg/g tissue ($p<0.05$), the level of IL-4, treatment was 214,8±22,6 pg/g tissue; after - 593,54±49,97 pg/g tissue. In the 3-rd group of patients, TNF-α prior to commencement of active therapy in exacerbation of the disease was 251,6±24,6; 2 months after treatment 418,2±35,2 pg/g tissue ($p<0.05$), INF-γ before the start of therapy was 237,6±30,1; 2 months since start of therapy left - 707,6±72,5 pg/g tissue ($p<0.05$); IL-4 changed from 277,2±24.6 to 400,4±39,8 pg/g tissue ($p<0.05$).

Conclusion

Under the influence of the MSCs, there is a gradual decrease of proinflammatory cytokines INF-γ, TNF-α to the 2-nd month of observation. The level of anti-inflammatory cytokine IL-4 after administration of MSCs also decreased.

AUTO1-0329
GASTRO INTESTINAL AUTOIMMUNITY

IMPAIRED SUPPRESSIVE FUNCTION OF LESIONAL REGULATORY T-CELLS COMPARED TO PERIPHERAL REGULATORY T-CELLS IN INFLAMMATORY BOWEL DISEASE

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Background

Inflammatory Bowel Diseases (IBD) are characterized by the infiltration of inflammatory B- and T-cells into the intestinal mucosa. Regulatory T-cells (Tregs), defined by CD4+CD25highFoxP3+, have been shown to be protective in specific autoimmune disorders, but the precise involvement of different subtypes and origins of Tregs in the pathogenesis of IBD is unclear. Therefore, the study aims to identify Tregs from IBD and to compare the phenotype and suppressive function of peripheral and lesional Tregs in order to understand the pathogenetic role of different Treg subtypes.

Method

Lymphocytes from peripheral blood and tissue samples from IBD patients undergoing surgery were characterized by flow cytometry. The ability of isolated peripheral and lesional Tregs (CD4+CD25+) to suppress proliferation of CFSE-labeled peripheral blood mononuclear cells (PBMCs) was investigated in suppression assays.

Results

Slightly increased proportions of Tregs were found in lesional tissue (1.5±1.0%) compared to peripheral blood (1.2±0.9%). The first population featured an enlarged production of the proinflammatory cytokine IL-17 ($p<0.01$). Whereas peripheral Tregs of IBD patients and healthy donors were similar in suppressive function, lesional Tregs were less successful to suppress PBMCs from the same IBD patient (14.3±12.9% suppression) than peripheral Tregs (40.5±14.3% suppression) ($p<0.01$).

Conclusion

In summary, despite the abundance of Tregs in IBD lesions, those Tregs were less sufficient to suppress PBMCs than Tregs derived from the periphery. In addition, lesional Tregs provide a higher inflammatory potential shown by intracellular pro-inflammatory cytokine production. In conclusion, peripheral and lesional Tregs may provide different functional capacities which may explain the excess of inflammatory PBMCs in IBD.

AUTO1-0531
GASTRO INTESTINAL AUTOIMMUNITY

EVALUATION OF ANTI-MAJOR ZYMOGEN GRANULE MEMBRANE PROTEIN AND ANTI-SACCHAROMYCES CEREVISIAE ANTIBODIES AS AN AID IN THE DIFFERENTIATION OF CROHN`S DISEASE AND ULCERATIVE COLITIS

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Background

The differentiation of Crohn`s disease (CrD) and ulcerative colitis (UC), the two forms of inflammatory bowel disease (IBD), can be challenging since many of the symptoms of both diseases are similar. There is a need for further diagnostic and prognostic biomarkers. While anti-*Saccharomyces cerevisiae* antibodies (ASCA) are more sensitive for CrD than UC or other diseases, antibodies to major zymogen granule membrane protein (MZGP2) have been found to be more specific. The objective of this study was to investigate both ASCA and autoantibodies towards MZGP2 in an IBD cohort.

Method

A total of 1157 patients were tested on a novel assays capable of detecting both IgA and IgG ASCA and anti-MZGP2 antibodies. The sample cohort consisted of 297 samples from patients with CrD, 81 samples from patients with UC, and 779 disease control samples.

Results

The prevalence of both anti-MZGP2 and ASCA (for IgG and IgA) were higher in CrD compared to UC and to other controls ($p<0.05$). ASCA IgG showed the highest sensitivity, while MZGP2 exhibited the highest specificity. Results are summarized in the table below.

Analyte	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95% CI)	LR- (95% CI)	Odds Ratio (95% CI)	Youden's Index	AUC (95% CI)
ASCA IgG	47.8% (42.2-53.5%)	80.0% 77.2-82.5%)	2.4 (2.0-2.9)	0.7 (0.6-0.7)	3.7 (2.8-4.9)	0.278	0.678 (0.642-0.715)
ASCA IgA	44.4% (38.9-50.1%)	85.5% (83.0-87.7%)	3.1 (2.5-3.8)	0.7 (0.6-0.7)	4.7 (3.5-6.3)	0.299	0.691 (0.654-0.729
ASCA IgG + IgA (dual +)	34.7% (29.5-40.3%)	92.3% (90.4-93.9%)	4.5 (3.4-6.0)	0.7 (0.6-0.8)	6.4 (4.5-9.0)	0.270	n/a
MZGP2 IgG	22.2% (17.9-27.3%)	96.4% (94.9-97.4%)	6.2 (4.1-9.2)	0.8 (0.8-0.9)	7.6 (4.9-12.0)	0.186	0.595 (0.556-0.635)
MZGP2 IgA	17.2% (13.3-21.9%)	96.7% (95.3-97.7%)	5.3 (3.4-8.2)	0.9 (0.8-0.9)	6.2 (3.8-10.0)	0.139	0.628 (0.590-0.667)
MZGP2 IgG + IgA (dual +)	11.4% (8.3-15.6%)	99.3% (98.5-99.7%)	16.4 (7.1-37.8)	0.9 (0.8-0.9)	18.4 (7.8-43.2)	0.108	n/a
ASCA + MZGP2 (dual +)	18.2% (14.2-23.0%)	96.3% 94.8-97.4%)	4.9 (3.2-7.4)	0.8 (0.8-0.9)	5.8 (3.6-9.1)	0.145	n/a

Of the 29 UC samples positive for ASCA, one was dual positive for both MZGP2 isotypes, while two were positive for IgA MZGP2 only. Of the 202 controls positive for ASCA, three were positive for both MZGP2 isotypes, while twelve were positive for IgG MZGP2, and 14 were positive for IgA MZGP2.

Conclusion

Antibodies to MZGP2 are highly specific for CrD, and together with the presence of ASCA, can aid in the differentiation of CrD and UC.

AUTO1-0135
GASTRO INTESTINAL AUTOIMMUNITY

IS THE USAGE OF THE PRE-ENDOSCOPIC SCREENING TEST FECAL CALPROTECTIN IN PRIMARY CARE A COST-SAVING TECHNIQUE IN PORTUGAL? A HEALTH ECONOMICS SIMULATION STUDY

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Background

The majority of bowel disorders exhibit overlapping symptoms, making diagnosis difficult in primary care (PC). Inflammatory bowel diseases (IBDs) are characterized by chronic inflammation of the gastrointestinal tract; irritable bowel syndrome (IBS) is a functional disorder (prevalence 10-20%). Endoscopy is the gold standard to diagnose IBD, but it turns negative in most cases due to IBD's low prevalence; moreover, endoscopy is expensive, uncomfortable and risky for the patient. F-Calprotectin is a fecal marker of intestine inflammation that can be used as a pre-endoscopic technique to rule out IBDs.

The present study aims at evaluating the cost-effectiveness of F-Calprotectin compared to the usage of serologic markers CRP and ESR, and to colonoscopy to distinguish IBD from IBS in Portugal in a PC setting.

Method

A 18-weeks health economics Markov model was developed for each diagnostic strategy, simulating 1000 patients presenting to PC with unspecific gastrointestinal symptoms. Diagnostic tests' sensitivities and specificities are listed in Table 1. Outcomes include cost savings, cost per corrected IBD diagnosed, and colonoscopies reduction.

Results

Table 1 shows that F-Calprotectin is cost-effective compared to CRP+ESR, and to colonoscopy; it:

1) results in more corrected IBD diagnoses at a lower price;
2) reduces the number of unnecessary endoscopies, increasing the number of correctly diagnosed IBD and IBS patients.

Conclusion

Results show that the usage of F-Calprotectin as pre-endoscopic diagnostic tool is associated with less colonoscopies, and important cost savings ascribable to reduced resource utilization. F-Calprotectin can be considered as good value for money if used in PC in Portugal.

AUTO1-0508
GASTRO INTESTINAL AUTOIMMUNITY

F-CALPROTECTIN HELPS REDUCING COSTS AND RISKS FOR PATIENTS IN THE DIAGNOSIS OF COLONIC PATHOLOGY: A PROSPECTIVE REAL-LIFE STUDY FROM THE CLINICAL HOSPITAL OF ZARAGOZA

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Background

Colonoscopy represents the gold standard in case of suspected colonic pathology. Colonoscopy has limited availability, brings about risks and is costly. F-Calprotectin can differentiate between organic/functional intestinal disorders, and could be a pre-endoscopic tool to identify patients not needing a colonoscopy.

This study aims to quantify the burden of colonoscopy in 404 consecutive unselected patients referred to colonoscopy by Primary Care (PC) or Secondary Care (SC) in Zaragoza, and to validate the pre-endoscopic usage of F-Calprotectin in the symptomatic population studied.

Method

Diagnosis was established by colonoscopic investigation; F-Calprotectin levels were evaluated with EliA-Calprotectin2 (cut-off=50mg/kg). Real-life data were prospectively collected. The actual situation was compared with two simulations in which F-Calprotectin was used to select which patients required further investigations.

Results

317 individuals (78.5%) were declared healthy after colonoscopy; 87 were affected by polyps (55), proctitis (7), IBD (14), colorectal cancer (11). Total costs were 329667€ (816€/patient); 2.5% of colonoscopies brought about complications, accounting for 6.0% of the total costs.

Simulation results show that F-Calprotectin reduced the cost/patient by 138€ (16.9%) if used in PC only, and by 247€ (30.3%) if used in PC+SC. Respectively, 10 (11.5%) and 19 (21.8%) patients with significant colon pathology were missed.

Conclusion

Results show that F-Calprotectin could be used to avoid colonoscopy in symptomatic patients without alarm symptoms; its usage is associated with less colonoscopies, less complications, and cost savings. The 3 cancer patients missed using F-Calprotectin would have undergone a colonoscopy anyhow, as aged above 50 and with rectal bleeding/anaemia.

AUTO1-0144
GASTRO INTESTINAL AUTOIMMUNITY

ANTI-GHRELIN AUTOANTIBODIES ARE DECREASED IN RHEUMATOID ARTHRITIS PATIENTS AND ARE RELATED TO METABOLIC CHANGES

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Background

Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with increased risk of cardiovascular diseases and metabolic alterations. The mechanisms underlying these alterations remain unclear. Ghrelin is a gastrointestinal hormone with potent regulatory effects on food intake, body weight and metabolism. Recent studies reported the presence of anti-ghrelin autoantibodies in healthy subjects and altered levels and affinity of these natural autoantibodies in anorectic and obese individuals. The aim of this study was to analyze the anti-ghrelin autoantibodies in RA patients and evaluate its relationship with metabolic, anthropometric and clinical parameters

Method

A cross-sectional study with 49 RA patients, 32 control subjects and 28 rheumatic controls was performed. An enzyme-linked immunosorbent assay (ELISA) was developed and validated for anti-ghrelin (IgG and IgA) autoantibodies quantification. Blood lipids (TC, HDL-C, LDL-C, TG) and glucose were determined by colorimetric-enzymatic methods and the body composition by electrical bio-impedance

Results

The RA patients had lower IgG anti-ghrelin autoantibodies levels and higher immune complexes percentage (IgG+ghrelin) in comparison to control subjects (p0.05), while the IgA anti-ghrelin autoantibodies showed no differences. The IgG+ghrelin immune complexes were negatively correlated with: weight (r=-0.260, p=0.02), BMI (r=-0.27,p= 0.01), fat percentage (r=-0.29,p=0.01), and TG (r=-0.44,p=0.03). The IgA anti-ghrelin autoantibodies correlated positively with RF (r=0.30,p=0.04), ACPA (r=0.29,p=0.05), ESR (r=0.37,p=0.008), DAS28 (r=0.29,p=0.05) and LDL-C (r=0.40,p=0.05)

Conclusion

Our findings show altered levels of IgG anti-ghrelin autoantibodies in RA patients and suggest a role of these natural autoantibodies in body weight and metabolism regulation. More studies are required to clarify the role and regulatory mechanisms of these autoantibodies

AUTO1-0503
GASTRO INTESTINAL AUTOIMMUNITY

IN SITU EXPRESSION OF IGA AND IGG IN INTESTINAL MUCOSA OF ALGERIAN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background

The intestinal mucosa is home to the largest population of Antibody-secreting plasma cells. The antibodies released by these cells constitute a first line of protection but could also be involved in autoimmune processes. Although the role of immunoglobulins in triggering inflammatory bowel disease (IBD) has not yet been established, there is many data to support this hypothesis. IBD including Crohn diseases (CD) and Ulcerative colitis (UC) is chronic multi-factorial disorder affecting the gastrointestinal.

Method

In this study, we investigated by immunohistochemical study the expression of IgA and IgG in the intestinal mucosa of Algerian patients with CD and UC

Results

Our results revealed the presence of a significantly high number of IgA + and IgG + cells for both categories of patients compared with healthy mucosa ($p<0.05$). The analysis of IgA and IgG expression at different regions of intestine of the patients did not show a significant difference. However our data, showed the presence of high number of IgA+ cells in the colonic mucosa of patients with CD in comparison with UC. This result could be explained by the strong expression of NOS-2 and TNF-α in CD that maintain IgA-producing plasma cells in the intestine. Moreover, a slight predominance of IgG + cells in the colonic mucosa of patients with CD was observed. This can be explained by the nature of the immune profile characterizing both pathologies.

Conclusion

In summary, the current study provides additional evidence for the Involvement of plasma cells secreting IgG and IgA in the pathophysiology of IBD.

AUTO1-0681
GASTRO INTESTINAL AUTOIMMUNITY

AUTOIMMUNE PANCREATITIS IS FORM OF CHRONIC PANCREATITIS ASSOCIATED WITH AUTOIMMUNE MANIFESTATIONS REVEALED ON LABORATORY, HISTOLOGICAL AND CLINICAL TESTING. WHICH IS RARE ENTITY.

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Background

Introduction

Autoimmune pancreatitis is an uncommon condition first formally described by Yoshida et al. in 1995. It is a form of chronic pancreatitis that is associated with autoimmune manifestations revealed on laboratory, histologic and clinical testing.[1] Due to its rarity, autoimmune pancreatitis remains an infrequently recognized entity. We present a case report of autoimmune pancreatitis in our institution.

Method

Case Report

A 51-year-old Chinese male diabetic, hypertension and hyperlipidemia, presented 2-weeks history of epigastric discomfort, jaundice and loss of weight of 7kg over 2months. Physical examination revealed deeply jaundiced, no palpable abdominal masses or lymphadenopathy.

Results

LFT showed cholestasic pattern. ALT>591,AST>292,ALP>681,GGT>1556

Investigations:

Serum IgG levels revealed elevated IgG 4 (>3.40g/L)

A CT Thorax, Abdomen and MRCP showed diffusely-enlarged pancreas with characteristic peripheral rim of hypo attenuating “halo”. MRI revealed T2 hyperintense focus in liver and multiple T1&T2 hypointense cortical lesions in both kidneys consistent with features of autoimmune pancreatitis with extra-pancreatic biliary and renal manifestations (IgG4-related disease).

Endoscopic US with FNA & ERCP showed distal CBD stricture and diffusely hypoechoic pancreatic parenchyma. Histology with IgG immune staining positive, supporting diagnosis of autoimmune aetiology.

Conclusion

Discussion

Patient underwent endoscopic sphincterotomy and stenting of commonbileduct, treated with corticosteroids with subsequent resolution of symptoms and normalized LFT. Although autoimmune pancreatitis is a rare condition, early recognition of characteristic features on laboratory and imaging investigations of this disease will result in prompt diagnosis and early, disease-specific intervention.

1.FinkelbergDL, SahaniD, DeshpandeV, BruggeWR. Autoimmune pancreatitis. NEJ Med2006; 355:2670.

[2] Autoimmune pancreatitis and IgG4-related systemic diseases, Int J Clin Exp Pathol. 2010; 3(5): 491–504. V

AUTO1-0132
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

PTPN22 GENE POLYMORPHISM IN ALGERIAN SYSTEMIC SCLEROSIS PATIENTS

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Background

Introduction.

The present study investigated whether protein tyrosine phosphatase 22 (PTPN22) gene polymorphism was involved in the genetic predisposition to **systemic sclerosis (SS)** in Algerian patients.

Method

Methods.

The PTPN22 (rs2476601) single nucleotide polymorphism (SNP) was directly genotyped in 117 SS patients and 120 healthy controls by real time -polymerase chain reaction method (TaqMan Assays). The relationships between anti-Scl70, anti-centromere and anti-topoisomerase antibodies positivity and genotypes were statistically analyzed.

Results

Results. The comparison of the allelic frequencies of the PTPN22 gene between patients and the control group shows a significant difference between patients and controls (0.42% vs 5% for the T allele, 99% vs 94% for the C allele, $P < 0.05$). The same result was showed for the genotype frequencies, a significant difference for the CC genotype and CT genotype was observed (99 vs. 90%, 0.85% vs. 9%, $P < 0.05$). The stratified analysis according to the antibodies positivity (anti-Scl70, anti-centromere and anti-topoisomerase) revealed no significant association with the PTPN22 alleles.

Conclusion

Conclusion. The functional polymorphism PTPN22 reported as associated with many autoimmune diseases seems to be involved in a genetic susceptibility to systemic sclerosis in the Algerian population.

AUTO1-0058
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

25-HYDROXYVITAMIN D3 DEFICIENCY AND VITAMIN D RECEPTOR POLYMORPHISMS IN EGYPTIAN BEHCET's DISEASE PATIENT: A PILOT STUDY

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Background

Vitamin D has an immunomodulatory action through binding to vitamin D receptor (VDR) which might be affected by VDR gene polymorphisms. We investigated serum levels of 25-hydroxyvitamin D3 and the VDR gene polymorphisms (FokI, BsmI) in Egyptian Behcet's disease patients and their relationship to disease manifestations and activity.

Method

45 Egyptian patients with BD fulfilling the international study group criteria ISG for BD (1999) and 45 matched controls were enrolled. Disease activity was measured using Behcet's disease activity index (BDAI). Patients who have two or more symptoms with worsening of clinical symptoms were considered active. Vitamin D status was defined as deficient <20 ng/ml and insufficient 20-30 ng/ml. VDR FokI, BsmI gene polymorphisms were evaluated using polymerase chain reaction and restriction enzyme cleavage.

Results

The serum levels of 25-hydroxyvitamin D3 were lower in BD group than control group (P = 0.006). Vitamin D3 deficiency was 6.7% vs 0%; respectively (P=0.012), and vitamin D3 insufficiency was 77.6% vs 60%; respectively (P=0.012). BsmI genotype frequencies were associated in BD group (P=0.001) with frequency of BB (33.3%) and Bb (60%). To the contrary, there was no contribution of the FokI to BD (P=0.128). There was no significant relation between 25-hydroxyvitamin D3 levels and active clinical manifestations. Also, no correlation with disease activity, BDAI, or duration was present. Furthermore, Bb and Ff genotypes were associated with vitamin D3 deficiency and insufficiency in BD group (P <0.001, 0.001 respectively).

Conclusion

lower serum level of 25-hydroxyvitamin D3 might be a modifiable risk factor in BD patients.

AUTO1-0969
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

AUTOIMMUNITY EPIGENESIS LUPUS INDUCED BY PREGNANCY

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Background

AUTOIMMUNITY EPIGENESIS
LUPUS/AUTOIMMUNITY INDUCED BY PREGNANCY

Not a gene, nor a genoma, nor an autoreactive cell, nor a lack of control of activation and regulatory mechanism of immune response but a scenario where the behaviour is autoagressive and this elicits autoimmunity on molecular level .

Method

I collected 3 cases of women who had been a fruit of unwanted pregnancy and suffered neglect or abandonment during their development as a personal self. Most likely, pregnancy would be an opportunity to recreate their space of daughter in the mother they want to be.
Unwanted pregnancy is auto aggressive for these women.

Results

In the emblematic case she had a normal pregnancy and a normal baby before the one in foccus.
In the second case she could have a second and NORMAL pregnancy afterwards.
The third case had just one pregnancy, the one that was unwanted. The lupus had a good prognostic for all patients
conclusion:
This is the plot for autoimmunity that appears in pregnant women: the conjuntural (unwanted pregnancy) beating the structural (unwanted pregnancy)

Conclusion

LUPUS INDUCED BY PREGNANCY

LUPUS that shows up for the first time, induced by pregnancy. Pregnancy is a scenario that gives origin to a baby, a father and a mother. The nine months is not only the time for development of an egg to a newborn, but it is also a time for the mental processing of the mother role in a pregnant woman. In this process the mind of a pregnant woman fits what Winnicot calls primary maternal preoccupation

AUTO1-0970
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

LUPUS IN ADOLESCENTS-ROOT CHILD

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Background

AUTOIMMUNITY EPIGENETIC FACTS

Adolescent Lupus - Root Child

Method

Selection of cases of Lupus in adolescents in a phase of identity formation . Interview with parents The space of the newborn in the parents is a principle that says where he come from, dictates the relationships among them and influence their fates,

Results

First case is a 17 year old white adolescent female that got lupus when she became aware of an extra conjugal life of her father. Her mother did not want a separation or divorce and got pregnant. The father told her that this significant other a long history that started befores her pregnancy. and the separation in this scenario sounded to him - not one between normal people but a double abandonment: the incapable wife and she, the expected baby.

Second case involved a 14 year old female who had a neurological presentation with seizures, skin lesion, cytopenia , artralgias, autoantibodies. She responded well to steroid and immuno supressors. Activity of the disease was dictated by the ups and downs between her parents. The disease supported the family life for over 4 years when the patient finally died.

Conclusion

Some adolescents develop lupus as a piece of his identity crisis. In the two cases presented here, they came to life as a root of the Family tree in order to maintain the mariage of their parents. They bring a karma: Be a bridge between them, support their relationship. This comes to be a challenge at the time of identity crisis.

AUTO1-0579
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

EXPRESSION OF IRF5 SNPS IS AT HIGH RISK OF DEVELOPING SLE AND RA IN ALGERIAN PATIENTS

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Background

Many IRF5 gene SNPs, a major regulator of the type I IFN induction, have been associated with connective tissue diseases onset such as SLE and RA. The aim of our work was to analyze possible contribution of IRF5 gene SNPs in SLE and RA susceptibility among Algerian patients.

Method

Our study included 155 SLE patients, 355 RA patients and 235 healthy controls. The IRF5 SNPs were genotyped using TaqMan® technology. We used Phase 2.1 software to generate haplotypes. IRF5 haplotypes based on the 3 SNPs tested were examined for association with SLE and RA.

Results

In our population, high susceptibility for SLE was associated with 2 IRF5 SNPs : allele T for IRF5 rs2004640 (-3835 G/T), allele C and genotype CC for IRF5 rs752637 (-2716 C/T). For RA patients, genotype CC was associated with high risk compared to healthy controls. Furthermore, ATC haplotype was at high risk for SLE and AGT was more frequent in healthy controls than SLE patients were. Otherwise, ACT haplotype was associated with anti-DNA and anti-SSA production. We have found a few reports suggesting association between IRF5 gene SNPs and autoantibody production in SLE. Finally, production of ACPA, in RA patients, was associated with IRF5 rs729302 (-13176 A/C) SNP expression.

Conclusion

Our results provide evidence-implicating IRF5 in SLE and RA susceptibility. We also demonstrated that IRF5 rs2004640 and rs752637 were associated with anti-ds DNA antibodies production in SLE patients and IRF5 rs729302 was associated with ACPA production in RA patients.

AUTO1-0907
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

MICRORNA-548AC MODULATES IMMUNOLOGICAL PROCESSES IN MULTIPLE SCLEROSIS BY TARGETING SDC4, SEL1L AND TNFAIP3

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Background

MicroRNAs regulate gene expression by destabilizing transcripts and/or repressing translation. The multiple sclerosis (MS)-associated CD58 gene locus encompasses the primate-specific microRNA hsa-mir-548ac. Genetic risk variants in this locus are linked to increased levels of mature miR-548ac. We aimed at identifying the target genes of this microRNA to contribute to the understanding of the molecular mechanisms by which the CD58 locus may affect MS susceptibility.

Method

HeLa cells were transfected with plasmids encoding the hsa-mir-548ac precursor to overexpress mature miR-548ac. The levels of mature miR-548ac 24h and 48h post transfection were measured with real-time PCR assays. Transcriptome profiling analysis was performed. Significantly downregulated transcripts were identified. Their relation to the mir-548 family was investigated. The most likely direct targets of miR-548ac were identified with bioinformatic methods and validated with luciferase assays.

Results

Transcriptome profiling analysis showed that 257 (24h) and 99 (48h) transcripts were significantly downregulated in HeLa cells in response to overexpression of miR-548ac. Of these, 53 transcripts were sequence-related to members of the mir-548 family. Ten transcripts were regarded as the most likely direct targets of miR-548ac. Among them were SDC4, SEL1L and TNFAIP3, for which validation experiments have confirmed direct interactions with miR-548ac. They have been associated with immunological processes before.

Conclusion

Our results imply an immunomodulatory role of miR-548ac. Many more MS-associated genetic loci are close to regions encoding human microRNAs. Studying their functions will further enhance the understanding of this immune-mediated disease. These efforts might also have implications for the identification of novel biomarkers in MS.

AUTO1-1009
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

ASSOCIATION OF 86 BP VNTR POLYMORPHISM OF INTERLEUKIN-1 RECEPTOR ANTAGONIST (IL1RN) WITH SYSTEMIC LUPUS ERYTHEMATOSUS SUSCEPTIBILITY IN MEXICAN-MESTIZO POPULATION

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Background

Interleukin-1 receptor antagonist (IL-1Ra) is an anti-inflammatory cytokine that override the pro-inflammatory effects of IL-1β. Several studies have reported polymorphisms in the interleukin-1 family associated with susceptibility to autoimmune diseases. In particular, a VNTR of 86 bp repeats (rs2234663) in the intron 2 of *IL-1RN* gene has been associated with susceptibility for rheumatoid arthritis in Mexican-Mestizo population.The aim of this study was to determine the association of 86 bp VNTR *IL1RN* polymorphism with systemic lupus erythematosus (SLE) susceptibility in Mexican-Mestizo population.

Method

This case-control study was conducted in 338 healthy subjects (HS) and 274 SLE patients classified according to the 1982 ACR criteria for SLE. Genotyping was performed by PCR technique.

Results

The 86 bp VNTR *IL1RN* polymorphism was found in Hardy-Weinberg equilibrium (p=1.0). Regarding the genotypic frequencies, differences were observed in their distribution (SLE vs HS; p=0.02). The most frequent genotypes were the A1/A1 (SLE=46% vs HS=56%) followed by the A1/A2 (SLE=44% vs HS=32%) and A2/A2 (SLE=8% vs HS=8%), other genotypes were observed with frequency <1%. The A1/A2 genotype was associated with 1.7 folds more susceptibility to SLE (OR=1.7; CI=1.2-2.4; p=0.002). Regarding the allelic frequencies, differences were observed by groups (p= 0.002) and the A2 allele confers 1.3 folds more susceptibility to SLE (OR=1.3; CI=1.02-1.73; p=0.02). The genotypes were grouped following a dominant genetic model, and the heterozygous condition for the A2 allele confers 1.63 folds more susceptibility to SLE (OR=1.63; CI=1.14-2.32; p=0.004).

Conclusion

The A1/A2 genotype and the A2 allele confers genetic susceptibility to SLE in Mexican mestizo population.

AUTO1-0095
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

NITRIC OXIDE SYNTHASE PROMOTER POLYMORPHISMS INCREASE RISK FOR CROHN'S DISEASE IN ALGERIAN MALES

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Background

Nitric oxide synthase (NOS) catalyses the production of nitric oxide (NO) which participates in inflammation and apoptosis seen in Crohn's disease (CD). The aim of this study is to identify the possible contributions of NOS2 -1659C/T, -1026T/G, -277A/G promoter polymorphisms towards development of CD in Algerian population.

Method

A total of 204 CD patients (113 females, 91 males) patients with CD (mean age 40.3 ± 13.4 years, disease duration 5.5 ± 4.3 years) and 201 age- and sex-matched healthy individuals were genotyped for promoter polymorphisms by TaqMan chemistry. Age of onset, location and disease behaviour and response to therapy were assessed for all patients. The three single nucleotide polymorphisms (SNPs) were in Hardy-Weinberg equilibrium.

Results

The frequency of AA genotype of NOS2-277 was higher in patients (pc = 0.04, OR = 4.02) compared to controls. Stratification by gender show strong association between genotypes AA of NOS2-277, GG of NOS -1026T/G, CC of -1659C/T and Crohn's disease in males' subgroup (pc = 0.04, OR = 4.02, pc = 0.04, OR = 4.02, pc = 0.04, OR = 4.02, respectively).
However, no significant difference in frequency of studied NOS2 polymorphisms was associated with clinical phenotypes.

Conclusion

The NOS2 -1659C/T, -1026T/G, -277A/G promoter polymorphisms in iNOS may confer susceptibility to CD in males.

AUTO1-0110
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

POLYMORPHISMS WITHIN THE HLA CLASS II GENE AS PROGNOSTIC FACTOR IN RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is a common inflammatory disease in which both genetic and environmental factors play a role in disease development. The aim of this study is to investigate the role of shared epitope (SE) alleles as risk factor to sever RA.

Method

A total of 205 RA patients (81% females) fulfilling ARA 1987 RA criteria, and 212 age- and sex-matched healthy individuals were genotyped for HLA DRB1 and HLA DQB1 using polymerase chain reaction and sequence-specific oligonucleotide (PCR-SSO). Disease Activity Score-28 (DAS28) activity measure treatment regiment were assessed for all patients.

Results

The frequency of HLA-DRB1*04 was found to be significantly higher in RA group compared to control, (30.3% vs 12%, pc=0.01, OR=3.26). HLA-DRB1*03 and *04 were associated to presence of anticitrulinated proteins (pc=0.001, OR=3.30 and pc=0.021, OR=3.02, respectively). Patients with active disease and erosive forms were HLA-DRB1*04 (pc=0.02, OR=5.33 and pc=0.04, OR=3.01, respectively).

Conclusion

HLA-class II gene can be potentially considered as genetic risk factor to RA and can predispose to aggressive forms.

AUTO1-0729
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

POLYARTHRITIS IN A PATIENT WITH TURNER SYNDROME

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Background

Turner syndrome is a hereditary disease that is caused by the lack of one X chromosome in some or all of the cells in female sex, which impedes sexual development and usually causes infertility. Polyarthritis is an inflammatory process in more than 4 joints at the same time which can have different etiologies.

Method

We report a case of a 32-year old woman from Serbia with a mosaic form of Turner syndrome who developed polyarthritis of unclear etiology.

Results

The patient had elevated CRP (C-reactive protein) and accelerated ESR (erythrocyte sedimentation rate). She was antiCCP (anti-cyclic citrullinated peptide) antibodies, RF (rheumatoid factor) and HLA (human leukocyte antigen) B27 negative. She responded very well on the application of glucocorticoids, In January 2017., after the consultation of the hepatologist (because of the prior elevation of liver enzimes), methotrexate has been included in the treatment and increased gradually up to 20 mg weekly. After three months, at the control, she felt much better, there were no clinical signs of active arthritis, and in the laboratory findings, for the first time, normal values of inflammatory syndrome markers were registered.

Conclusion

In the patient with Turner syndrome, the development of polyarthritis of unclear etiology occurred. Clinical picture with polyarthritis, hand and foot tenosynovitis and a very good response to methotrexate and corticosteroids therapy, confirmed our hypothesis that the patient had seronegative rheumatoid arthritis.

AUTO1-0146
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

ASSOCIATION OF MITOCHONDRIAL DNA COPY NUMBER WITH DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

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Background

Mitochondrial biology are associated with inflammation. Alteration of mitochondrial DNA copy number, which reflects oxidant-induced cell damage, has been observed in a wide range of human diseases. Here we examined the comparison of the mitochondrial DNA copy number between rheumatoid arthritis (RA) patients and healthy controls (HC).

Method

41 RA patients and 45 age- and sex-matched healthy controls were recruited. There were 15 patients of clinical remission group with DAS28-ESR≤2.6 and 20 patients of non-clinical remission group with DAS28-ESR>2.6. The mitochondrial DNA copy number was measured by a quantitative real-time PCR assay using DNA extracted from peripheral blood.

Results

The analyses show significant differences in mitochondrial DNA copy number between RA and HC (mean of RA=101.71, interquartile range (IQR): 71.84-154.08; mean of HC=140.56, IQR: 103.43-195.07; p value=0.012). By disease activity, however, mitochondrial DNA copy number of clinical remission group was not different from non-clinical remission group (p value=0.268).

Conclusion

Our results suggest that the more mitochondrial DNA copy number is one of the characteristics of rheumatoid arthritis compared with healthy controls.

AUTO1-0677
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

POLYMORPHISM 10C/T AND 25G/C OF THE TGF-B1 GENE IN ALGERIAN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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Background

Introduction:
Autoimmune thyroiditis (AIT) is one of the most common organ-specific autoimmune diseases, with Hashimoto's thyroiditis (HT) and Graves-Basedow's disease (GB), the most common clinical expressions. Cytokines play a crucial role in the pathogenesis of AIT as they are key regulators of the immune and inflammatory response; and therefore polymorphisms at the genes encoding cytokines are potential risk factors for the development of AIT.

Method

The SNPs polymorphisms 10C/T and 25G/C of the TGF-B1 cytokine gene was studied by PCR-SSP. This was a case-control study of 41 patients with autoimmune thyroiditis (27 HT and 14 GD) and 35 healthy subjects in the control population.

Results

The High Phenotype of the TGF-β was associated in women with susceptibility to AI T (OR = 3.47, IC [0.94-13.50], p = 0.034) while the intermediate phenotype was protective in women (OR =0.27, IC [0.06-1.05], p = 0.032).

Conclusion

TGF-B gene polymorphisms are involved in susceptibility to AIT in women.

AUTO1-0684
GENETICS AND EPIGENETICS IN AUTOIMMUNITY

POLYMORPHISM -308 OF THE TNF-A GENE IN ALGERIAN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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Background

Autoimmune thyroiditis (TAI) is one of the most common organ-specific autoimmune diseases, with Hashimoto's thyroiditis (TH) and Graves-Basedow's disease (GB), the most common clinical expressions. TH is characterized by hypothyroidism associated with thyroid destruction by thyroglobulin-specific self-reactive T lymphocytes. In contrast, GB disease , is characterized by hyperthyroidism due to excessive production of thyroid hormones induced by thyrotropin receptor-specific autoantibodies. Cytokines are key regulators of the immune and inflammatory response; and therefore polymorphisms at the genes encoding cytokines are potential risk factors for the development of TAI.

Method

The SNP polymorphism of the gene of proinflammatory cytokine TNF-α-308 A / G was studied by PCR-SSP. This was a case-control study of 41 patients with autoimmune thyroiditis (27 HT and 14 GD) and 35 healthy subjects in the control population.

Results

The AG genotype of the TNF A-308A / G was more common in TAI vs. control (OR = 3.29, IC [1.02-11.04], p = 0.048) and in TH patients (OR = 3.87, IC [1.06-14.94], p = 0.039).

Conclusion

Our study reports an association between the polymorphism of the TNF-α gene and the development of TAI, highlighting the relevance of the polymorphisms of genes related to inflammation in the etiopathogenesis of TAI.

AUTO1-0842
HEMATOLOGICAL DISEASE AND AUTOIMMUNITY

AUTOIMMUNE MOSAIC: DIVERSE;? CONVERSE? OR VERSE?

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Background:
Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare paraneoplastic disease secondary to plasma cell dyscrasia.
Methods:
We assessed the clinical characteristics of a 53-year-old woman who developed atypical POEMS syndrome with idiopathic portal hypertension and thrombocytopenia.
Results:
The first clinical manifestation of the disease was sensorimotor peripheral neuropathy and the patient was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). Later, she developed significant thrombocytopenia and was diagnosed with idiopathic thrombocytopenic purpura (ITP). Following treatment with steroids and IVIG, significant clinical improvement was achieved in CIDP and ITP.
After steroids withdrawal, she developed significant weight loss, generalized pruritus, peripheral edema, and pericardial and pleural effusions followed by intractable ascites. Repeated CT and PET scans revealed massive splenomegaly, mild lymphadenopathy, ascites, a mixed sclerotic and lytic lesion in the right clavicle, and an area of sclerosis in the right 6th rib.
Gastroscopy showed esophageal varices, but repeated MRCPs and liver biopsy didn't reveal any definitive liver disease. Catheterization of liver veins demonstrated mild portal hypertension. Bone marrow biopsy showed plasma cell dyscrasia with IgA lambda monoclonal protein. Treatment with prednisone at a dosage of 20 mg/day along with diuretics and ursolate resulted in significant clinical improvement with resolution of ascites and pleural and pericardial effusions. The patient is a candidate to autologous peripheral blood stem cell transplantation. To date, only five cases of POEMS syndrome with portal hypertension have ever been reported.
Conclusion:
Physicians should be aware of the possible connection between POEMS and portal hypertension.

AUTO1-0825
HEMATOLOGICAL DISEASE AND AUTOIMMUNITY

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS COMBINATION THERAPY-INDUCED SEVERE PANCYTOPENIA IN A PATIENT WITH RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) treatment includes medications that slow the progression of joint damage from rheumatoid arthritis. These drugs are called disease-modifying antirheumatic drugs (DMARDs) and methotrexate (MTX) has been the hallmark of standard of care. Since many RA patients continue to have active disease, despite maximal doses of MTX, combinations with other DMARDs have provide improved clinical benefit for those patients. However, hepatotoxicity, leukopenia and infection risk, may increase when MTX are used in combination with other DMARDs because of additive toxicity.

Method

Here, we describe a 71 year-old patient who was being treated with MTX (15mg/week), Leflunomide (20 mg/day) and Etarnecept (50 mg/week) and develops septic shock due to urinary tract infection, with severe pancytopenia (hemoglobin: 64g/l, leucopenia: 0.2×10^9/l, platelets: 7×10^9/l). She was admitted at the Intensive Care Unit with Multiple Organ Dysfunction. The patient was treated with antibiotics, red blood cell transfusion and granulocyte colony-stimulating factor. Orogastric cholestyramine washout was also given to expedite the removal of the drug.

Results

The condition of the patient improved, and white blood cell, hemoglobin and platelet levels increased two weeks later. Although the recovery of this patient was due to combination of organ supportive care and antimicrobial therapy, removal of leflunomide may have improved her outcome.

Conclusion

The management of RA requires aggressive treatment with DMARDs, early in the disease course, before irreversible damage occurs. Knowledge of the patients comorbidities and the potential toxicities of the different DMARDs are key important for making informed decisions about the benefits and risks of the treatment.

AUTO1-0910
HEMATOLOGICAL DISEASE AND AUTOIMMUNITY

KIMURA DISEASE: A RARE CAUSE OF SUBCUTANEUS MASS AND LYMPHADENOPATHY

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Background

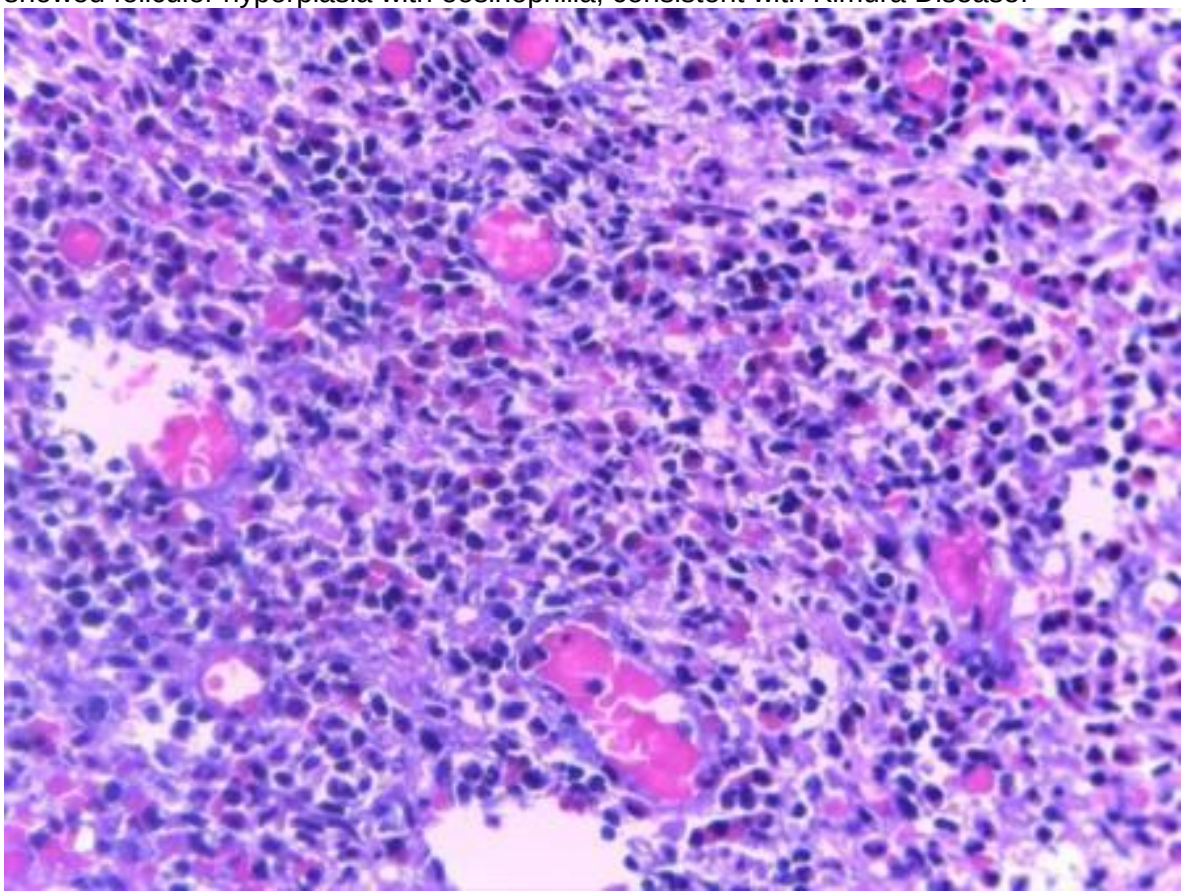
Kimura disease is a rare inflammatory condition characterized by subcutaneous mass and lymphadenopathy in the head and neck region. Elevated serum immunoglobulin E levels and peripheral blood eosinophilia are also common.

Method

Case Illustration

A 51 year old male complained a recurring lump under his right jaw since 1 year ago. He had another lump in the same location that was surgically removed 5 years ago. Other masses also grew in front of his left ear and on his right chest. On examination, there were firm, non-tender, and immobile subcutaneous masses in the right submandibula and left post aericula, with diameter 5 cm and 8 cm, respectively. There was a firm and immobile lymphadenopaty in the left cervical, with diameter 3 cm. Blood test revealed hypereosinophilia (2350/µl) and hyper IgE (26088 ng/mL). Histological examination

showed foliculer hyperplasia with eosinophilia, consistent with Kimura Disease.



Results

Discussion
Kimura disease is a benign, chronic inflammatory condition often producing subcutaneous tumor-like, painless nodules with a predilection in the head and neck region. It is found more often in Asian male, with peak age at the third decade. Histologically, the lesion is characterized by lymphoid hyperplasia, significant infiltration of eosinophils, and proliferation of capillaries. Although the pathophysiology for this disease is unkown, promoted Th2 responses are suggested to be responsible. The management for Kimura disease includes surgery, medication, and radiation. Steroids, both topical and systemic, have been shown to be transiently effective.

Conclusion

Kimura disease is a rare disease characterized by subcutaneus nodules and lymphadenopathies, elevated serum IgE, and eosinophilia.

AUTO1-1025
HEMATOLOGICAL DISEASE AND AUTOIMMUNITY

WALDENSTRÖM MACROGLOBULINEMIA IN THE PATIENT WITH PSORIATIC ARTHRITIS TREATED WITH METHOTREXATE AND TUMOR NECROSIS FACTOR ALPHA (TNFALPHA) INHIBITOR

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Background

Waldenström Macroglobulinemia is lymphoplasmic hyperplasia with excessive production of monoclonal M-protein. According to literature data, patients with psoriasis have more frequent lymphomas than healthy population. The real risk of lymphoproliferative disease in psoriatic arthritis patients has not yet been defined.

The aim of the study was to describe a case of a patient with psoriatic arthritis and concurent monoclonal gammopathy, who did not respond to treatment with TNFalpha inhibitor in combination with methotrexate.**Method**

A 57 year old woman with psoriasis and psoriatic arthritis diagnosed in 2012 with monoclonal gammopathy of undeterminated significance, was treated with non-steroid anti-inflammatory drugs, methotrexate (20mg once a week), folic acid 15mg and inhibitor of TNFalpha.

At the beginning of biological therapy she presented with laboratory results: ESR 126, total protein 8g/dl**,** abnormal IgM 11,6g/l , IgG 2,25g/l, IgA 0,32g/l. Immunofixation test revealed possitivity for IgM kappa monoclonal protein. There were no abnormalities in the bone marrow aspiration biopsy, no lymphadenopathy was observed. She complained of general weakness and polineuropathy. Analysis of spino-cerebral fluid showed type V of oligoclonal band.

Results

In 2017, after 2 years of TNFalpha inhibitor combined with methotrexate therapy, the diagnosis of Waldenstrom macroglobulinemia has been done. The patient presented with high ESR 103 and monoclonal IgM 33g/l**.** Repeated aspiration bone marrow biopsy showed 3% of plasmocytes and 21% of lymphocytes.
The patient started standard RCD chemotherapy regimen (rituximab, cyclophosphamide, dexamethason) with good clinical response to therapy.

Conclusion

Patients with psoriatic arthritis and high ESR treated with TNFalpha inhibitors should have immunoelectrophoresis monitored.

AUTO1-0578
HEMATOLOGICAL DISEASE AND AUTOIMMUNITY

MACROPHAGE ACTIVATION SYNDROME IN A CASE OF DERMATOMYOSITIS OVERLAPPING SYNDROME WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A CASE REPORT

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Background

Macrophage activation syndrome (MAS) is a rare but aggressive life-threatening auto-immune disease. It is characterized by fever, rash, splenomegaly, blood cytopenia, hypertriglyceridemia, high ferritin levels, liver insufficiency, coagulopathy and neurologic involvement. Persistent activation of inflammatory cells can lead to a cytokine storm and multi organ damage. MAS is usually triggered by rheumatologic diseases and rarely in the presentation of a new connective disease like systemic lupus erythematosus (SLE). In addition to MAS, the auto-immune conditions of SLE can be associated with different overlapping syndromes notably dermatomyositis.

Method

We present a 31 years old male from a Latin-American background without pre-existent conditions who presented complains of sore throat, joint pain, fever and fatigue. He quickly developed a pancytopenia with increased liver and pancreatic enzymes.

Results

We proceeded with a bone marrow biopsy which detected an active MAS. Regarding his muscle weakness, we also revealed an inflammatory myositis on a quadricep muscle biopsy. Further discovery of positive auto-antibodies (ANA and anti-DNA) showed the presence of a LED. We successfully treated this severe form of MAS with the HLH-2004 protocol (high doses of dexamethasone, etoposide and cyclosporine) and intravenously immunoglobulins. After 2 months of hospitalization and 12 days passed in the intensive care unit, the patient returned home with minimal sequelae with a long term immunosuppressive treatment of prednisone, mycophenolate mofetil and hydroxychloroquine.

Conclusion

Clinically stable forms of MAS are treated with the standard immunosuppressive targeted for each specific rheumatologic condition. In the other hand, severe forms of MAS should be treated aggressively with HLH-2004 protocol.

AUTO1-0597
IL17, TH17 AND AUTOIMMUNITY

ROLE OF TH17 CELLS AND IL-17, IL-23 CYTOKINES IN THE PATHOGENESIS OF AUTOIMMUNE THYROID DISEASE IN CHILDREN

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Background

Despite wide interest, the role of Th17 cells in the pathogenesis of inflammatory and autoimmune diseases is still being debated. Th17 cells are involved in immune responses against extracellular pathogens and have the ability to secrete cytokines: IL-17 and IL-23. Th17 cells can be characterized by several surface markers, i.e. CCR6 (CD196), IL-23R, IL-12Rbeta2 and CD161.The aim of the study was to estimate the proporcions of circulating CD4+CD161+CD196+ and CD4+IL-17+Th17 cells and serum concentrations of IL-17 & IL-23 in patients with Graves' disease (GD, n=22,14.3 ± 4 years), Hashimoto's thyroiditis (HT, n=37, 15±2 yrs) and in healthy controls (C, n=25,15.2 ± 2 yrs).

Method

Polychromatic flow cytometry and several fluorochrome-conjugated monoclonal antibodies were applied to delineate Th17 cells with either CD4+CD161+CD196+or CD4+IL-17+phenotype using apparatus FACSCalibur (BD Biosciences). The expression of IL-17 and IL-23 were analyzed by Bio-Tek ELx800 ELISA reader.

Results

In untreated HT children we observed an increased percentage of CD4+CD161+CD196+ ($p<0.04$) and CD4+IL-17+($p<0.01$) Th17 lymphocytes in comparison to the healthy controls. In GD children we did not reveal such abnormalities in the population of these cells. In untreated patients with AITD we observed an increased levels of IL-23 in comparison to control group (GD $p=0.004$, HT: $p=0.046$). Methimazole treatment in GD led to decrease these cytokine levels in a period of 6-12months.

Conclusion

We conclude that the increased percentage of Th17 cells and elevated level of IL-17 and IL-23 cytokines in children with HT can suggest their role in initiation and development of immune and inflammatory processes in this endocrinopathy.

AUTO1-0989
IL17, TH17 AND AUTOIMMUNITY

INFLAMATION, IL17 AND THYROID AUTOIMMUNITY IN PATIENTS WITH FIBROMIALGIA

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Background

The aim of the study is to investigate the link between some inflammatory markers, thyroid autoimmunity and pain threshold in patients with fibromyalgia.

Method

In the study were included 43 women with fibromyalgia with mean age 46.1±10.5 years. Of them 23 were in the age range 43-49 and 18 healthy controls. Twenty three (53,5%) of the women were menopausal, none of them took hormone replacement therapy. 74.4% of the included women were euthyroid, 23.1% - hypothyroid (10.3% drug compensated, 12.3 noncompensated) and only one woman was hyperthyroid.

Results

We cannot confirm the presence of significant link between interleukin 17 and autonomic neuropathy in patients with osteoartrosis and fibromyalgia (p=0.237), there is a marled correlation. There was no significant link between IL17 levels between patients with fibromyalgia and healthy controls despite the tendency towards higher levels in FM (33.1±128.7 vs. 9.1±9.8). This results present that thyroid status assesment is important in patients with fibromialgia. There is no difference in IL17 levels between patients with and without thyroid autoimmunity. There is no significant correlation between LI17 and TSH levels. The clinical observation and assessment of patients leads to practical results, linked to establishment of hypothyroidism as a reason for fibromyalgia in more than 30% of the patients. Levels of interleukin 17 is higher in patients with fibromyalgia than in controls.

Conclusion

This shows that the presence of inflammatory process can be linked to the clinical signs in patients with fibromyalgia and this is a component of the mixed pain in fibromyalgia.

AUTO1-0431
IL17, TH17 AND AUTOIMMUNITY

G-MDSC DERIVED EXOSOMAL MIR-93-5P ATTENUATE COLLAGEN-INDUCED ARTHRITIS BY REGULATING TH17 CELLS

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Background

Myeloid-derived suppressor cells (MDSC) have been described in rheumatoid arthritis (RA), but their role in the disease remains controversial. Exosomes play key roles in intercellular signaling, and involved in immune response.

Method

Here, we sought to define the effect of granulocytic MDSC-derived exosomes (G-MDSC exo) in collagen-induced arthritis (CIA) mice.

Results

G-MDSC exo-treated mice showed greater resistance to arthritis. There was a decrease in the proportion of Th17 cells in G-MDSC exo-treated CIA mice. In addition, G-MDSC exo could suppress the differentiation of Th17 cells in vitro. Exosomal miRNA expression profiles were analyzed by microRNA array, higher levels of miRNAs are encapsulated in G-MDSC exo. The miR-93-5p derived from G-MDSC exo could inhibit the differentiation of Th17 cells through targeting of STAT3 in vitro. Furthermore, knockdown of G-MDSC derived exosomal miR-93-5p couldn't attenuate arthritis in CIA mice.

Conclusion

Taken together, these results suggest that G-MDSC derived exosomal miR-93-5p attenuate CIA progression through inhibiting Th17 cells proliferation.

AUTO1-0299
IMMUNOMODULATION

FIRST EVIDENCES OF IMMUNOMODULATORY ACTIVITIES OF TUFTSIN-PHOSPHORYLCHOLINE ON SAMPLES FROM PATIENTS WITH GIANT CELL ARTERITIS IN COMPARISON TO CORTICOSTEROIDS

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Background

Tuftsin-PhosphorylCholine (TPC) is a novel bi-specific molecule which has shown immunomodulatory activities in experimental mouse models of autoimmune diseases. The present study aimed to investigate the therapeutic potential of TPC in giant cell arteritis (GCA), an inflammatory disease of large- and medium-sized arteries.

Method

Effects of TPC were determined *in vitro* on peripheral blood mononuclear cells (PBMCs) and temporal artery biopsies (TABs) obtained from three patients with GCA with inflamed TABs and three patients with normal TABs who received a different diagnosis. Patients were naïve from therapy. TPC was provided by TPCera (Jerusalem, Israel). Treatment with the corticosteroid dexamethasone was included as the standard of care. After treatments, levels of several cytokines in culture supernatants, PBMC viability and T helper (Th) cell differentiation were analyzed.

Results

Treatment with TPC significantly decreased IL-1β, IL-9, IL-12(p70), IL-13, IL-23 (>75%) and IL-2, IL-5, IL-6, IL-17A, IL-18, IL-21, IL-22, IFNγ, TNFα, GM-CSF (25-75%) in supernatants of CD3/CD28 activated PBMCs without affecting PBMC viability. It slightly inhibited Th1 and Th17 differentiation while did not impact Th22 differentiation induced by phorbol 12-myristate 13-acetate plus ionomycin. It had similar effects on PBMCs from patients with and without GCA. In inflamed TABs, treatment with TPC decreased IL-1β, IL-6, IL-13, IL-17A and IL-18 in culture supernatants. Effects of TPC treatment were mainly comparable to the effects of dexamethasone both in PBMCs and TABs.

Conclusion

TPC remarkably down-regulated the production of various pro-inflammatory cytokines by human samples *in vitro*, further emerging as a promising immunotherapeutic agent.

AUTO1-0372
IMMUNOMODULATION

LONG-TERM EVALUATION OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN ADMINISTRATION IN A LARGE SERIES OF ITALIAN PATIENTS

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Background

CVID is the most frequent symptomatic primary immunodeficiency (PID) of the adulthood. Treatment is based on intravenous (IVIg), subcutaneous (SCIg) and, more recently, facilitated subcutaneous immunoglobulin (f-SCIg). Our aim is to present data related to efficacy and safety of f-SCIg in patients with CVID from three different centers in Italy (Ancona, Pisa and Brescia).

Method

In this Italian multi-center study we describe 28 patients (16 F, 12 M, mean age 42 years) enrolled from November 2014. Diagnosis of CVID was according to ESID criteria. Twenty-one patients had recurrent infections only, whereas two had previous malignancy. These patients received a standardized protocol of monthly infusion of f-SCIg (20-40 g monthly). Four other patients had autoimmune thrombocytopenia (ITP), and one autoimmune hemolytic anemia (AIHA); they received fSCIg 20g every two weeks.

Results

All patients achieved and maintained protective serum IgG level. Nobody developed severe infections, but only mild upper-airways ones. In ITP, we observed a progressive platelet count increase; the patient with AIHA once reached remission could reduce the daily prednisone dose**.** No systemic adverse reactions linked to fSCIg were observed.

Conclusion

The administration of f-SCIg constitutes an effective, safe and well-tolerated replacement thepaeutic option in patients with CVID. Moreover, due to the positive action on autoimmune cytopenias, we can speculate about an immunomodulatory effect of f-SCIg.

AUTO1-0370
IMMUNOMODULATION

NEUROLOGIC AUTOIMMUNE DISORDERS IN COURSE OF PRIMARY ANTIBODY DEFICIENCIES

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Background

Primary antibody deficiencies (PADs) are a heterogeneous group of disorders with impaired antibody production. Infectious and autoimmune neurological complications in PADs are rarely described.

Method

We report three women with PADs and neurological autoimmune disorder. The first patient (F/71y) came to our attention for sensory ataxia, paraparesis, dysesthesia of lower limbs and neurogenic bladder with diagnosis of autoimmune myelitis. The second one (F/57 ys) presented with Devic syndrome: atasso-spastic gait, tetra-hyperreflexia and neurogenic bladder with the positivity of anti-aquaporin-4-antibodies. In both patients we detected recurrent infections with decreased serum immunoglobulin levels and impaired specific antibody responses, consistent with the diagnosis of common variable immunodeficiency. The third patient (F/43 ys), suffering from recurrent infections of subcutaneous tissue, developed a post-infectious acute myelitis after a pneumonia, with residual paraparesis and neurogenic bladder. Analysis documented a marked decrease in serum IgG3 levels.

Results

All patients were treated with high dose of intravenous immunoglobulin (IVIg;2 g/Kg/month). After three months while in remission patients 1 and 3 were switched to 20%subcutaneous immunoglobulin (20%SCIg). Patient 2 maintained IVIg replacement therapy (30g/month). Treatment was effective and well tolerated. At three years of follow-up, no neurological relapse occurred.

Conclusion

In literature there have been few reports on neurological autoimmune disorders in PADs. In these conditions treatment with high dose of immunoglobulin seems to be effective, thanks to the immunomodulant action of IVIg. Moreover replacement therapy with both IVIg or SCIg seems to prevent the reoccurrence of neurological autoimmune manifestations.

AUTO1-0694
IMMUNOMODULATION

WHICH ROLE FOR IMMUNOGLOBULIN IN PATIENTS WITH CANCER?

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Background

Human immunoglobulin (Ig), firstly used as replacement therapy in primary immunodeficiencies, has been given successfully to patients with different autoimmune diseases (AID). Available commercial preparations encompass polyclonal IgG pooled from sera of thousands of donors which can be administrated by the intravenous (IVIg) or subcutaneous (SCIg) route. Several mechanisms of action have been proposed to explain the mechanisms of IVIg-mediated immunomodulation, accordingly to the nature of the disease. The immunodulatory role of SCIg is not completely understood. Among the different properties of human Ig, it is possible to speculate about an immunomodulatory role even for patients with cancer. Natural antibodies in human Ig can have anti-tumorigenic functions that act especially on tumour spread.

Method

We presented a case of a patient (M/60 ys) with common variable immunodeficiency treated with IVIg 400 mg/kg monthly, then shifted to 20%SCIg (30 g/kg/week) for a major cardiovascular event. He was diagnosed with pancreatic cancer involving the isthmus and the body with diffusion to mediastinic lymph nodes. The prognosis was extremely severe.

Results

He received chemotherapy with Irinotecan, 5-fluorouracil and folinic acid while continuing 20%SCIg therapy. Eleven months after, he died for massive disease diffusion.

Conclusion

The treatment allowed him a longer survival; it is possible that Ig therapy lessen the disease spread and death. This anti tumorigenic function of Ig may represent a powerful adjuvant for inhibition of tumor spread. However, more data are needed to establish definitive conclusions.

AUTO1-0167
IMMUNOMODULATION

TOLEROGENIC EFFECTS OF ETHYL PYRUVATE ON DENDRITIC CELLS

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Background

Dendritic cells (DC) are responsible for initiation and modelling of an immune response. Tolerogenic DC (tolDC) induce regulatory T cells and promote regulatory immune response that counteracts autoimmunity. Therefore, tolDC are suitable for cell based immunotherapy of autoimmune disorders, including multiple sclerosis. Ethyl pyruvate (EP) is a redox analogue of dimethyl fumarate (Tecfidera), a drug for multiple sclerosis treatment. We have recently shown that EP ameliorates experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis through restrain of autoimmune response directed against the central nervous system. Here, its *in vitro* tolerogenic effect on mouse bone marrow derived dendritic (BMDC) cells was investigated.

Method

Bone marrow cells obtained from NOD mice were cultured for 7 days in the presence of granulocyte-macrophage colony-stimulating factor (GMCSF, added every other day). For generation of mature DC additional stimulation with LPS for 24h was performed. EP-treated DC were additionally exposed to 3.1mM EP added simultaneously with GM-CSF.

Results

EP-treated DC had lower expression of molecules required for T cell activation, including MHC class II molecules and co-stimulatory proteins CD40 and CD86 in comparison to mature DC. Importantly, EP did not affect expression of a DC marker CD11c. Further, DC treated with EP showed decreased production of pro-inflammatory cytokines: IL-12, IL-1beta, IL-6 and TNF.

Conclusion

These results imply that EP directs DC towards tolDC. Further studies on the tolerogenic effects of EP on DC, as well as on potential application of EP-induced tolDC *in vivo* are warranted.

AUTO1-0777
IMMUNOMODULATION

PCSK9 PLAYS A NOVEL IMMUNOLOGICAL ROLE IN THE OXIDIZED LDL-INDUCED DENDRITIC CELL MATURATION AND T CELL ACTIVATION FROM HUMAN BLOOD AND ATHEROSCLEROTIC PLAQUE

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Background

Activated T cells and dendritic cells (DCs) occur in atherosclerotic plaques. Proprotein convertase subtilisin kexin 9 (PCSK9) targets the LDL-receptor (LDLR), and results in increased LDL-levels. We here investigate immune effects of PCSK9 on OxLDL induced DC maturation and T cell activation.

Method

T cells were isolated from carotid specimens of patients undergoing carotid endarterectomy, or from peripheral blood of healthy individuals. Human peripheral blood monocytes were differentiated into DCs. Naïve T cells were co-cultured with pretreated DCs. The effects of PCSK9 and its inhibition by silencing were studied.

Results

OxLDL induced PCSK9 in DCs and promoted DC maturation with increased expression of CD80, CD83, CD86 and HLA-DR and the scavenger receptors LOX-1, CD36 and SR-A. T cells exposed to OxLDL-treated DCs proliferated and produced IFN-γ and IL-17, thus with polarization to Th1 and/or Th17 subsets. Silencing of PCSK9 reversed the OxLDL effects on DCs and T cells. DC maturation was repressed and the production of TNF-α, IL-1β and IL-6 was limited, while TGF-β and IL-10 secretion and T regulatory cells were induced. OxLDL induced miRNA let-7c, miR-27a, miR-27b, miR-185. Silencing PCSK9 repressed miR-27a and to a lesser extent let-7c. PCSK9 silencing enhanced SOCS1 expression induced by OxLDL. Experiments on T cells from carotid atherosclerotic plaques or healthy individuals showed similar results.

Conclusion

We demonstrate immunological effects of PCSK9 in relation to activation and maturation of DCs and plaque T cells by OxLDL, a central player in atherosclerosis. This may directly influence atherosclerosis and cardiovascular disease, independent of LDL-lowering.

AUTO1-0642
IMMUNOMODULATION

ICOS-LIGAND TRIGGERING INHIBITS OSTEOCLAST FUNCTION IN VITRO AND IN VIVO.

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Background

Bone loss due to hyperactivation of osteoclasts (OCs) is a common feature of several chronic inflammatory and autoimmune diseases since the risk of osteoporosis is increased in patients with rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus. ICOS ligand (ICOSL) is the ligand of the ICOS T cell costimulatory molecule, and it is expressed in haematopoietic e non-haematopoietic cells. The ICOSL:ICOS interaction triggers bidirectional signals which are able to modulate the response of both the cells expressing ICOS and those expressing ICOSL.

Method

This work stems from our finding that OCs (differentiated *in vitro* from monocytes) can express ICOSL, and it was aimed to investigate the effect of ICOSL triggering on differentiation and function of OCs *in vitro* and *in vivo*.

Results

The *in vitro* results showed that ICOS-Fc inhibits OCs differentiation by inhibiting the acquirement of the OCs morphology, the $CD14^-$ Cathepsin K^+ phenotype, and the expression of tartrate resistant acid phosphatase, OSCAR, NFATc1, and DC-STAMP. Moreover, ICOS-Fc induces a reversible decrease in the sizes of cells and number of nuclei and Cathepsin K expression in mature OCs. Finally, ICOS-Fc inhibits the osteolytic activities of OCs. The *in vivo* results showed that the treatment with ICOS-Fc strikingly inhibited the development of bone loss in soluble RANKL treated mice and in ovariectomized mice, both mouse models of osteoporosis, with a prophylactic and therapeutic effects.

Conclusion

These data open a novel field in the pharmacological use of agonists and antagonists of the ICOSL:ICOS system and detected a novel molecular system involved in osteoimmunology.

AUTO1-0282
IMMUNOMODULATION

IMMUNOMODULATORY EFFECTS OF D-MANNOSE

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Background

Dendritic cells are the major antigen-presenting cells of immune system and together with macrophages have a key role in initiation and propagation of (auto)immune response. Immunomodulation of these cells to tolerogenic phenotype is one of the main approaches in current therapy strategies for autoimmune disorders. D-mannose is a natural carbohydrate found in many plants. It is important in animal metabolism, especially in the glycosylation of certain proteins. The aim of this study was to examine effects of D-mannose on dendritic cells and macrophages.

Method

For this purpose, immature DC (iDC), mature DC (mDC) and D-mannose induced DC were generated in presents of GM-CSF from rat bone marrow cells. Macrophages were collected by peritoneal lavage and treated with the D-mannose. Functional status of cells was estimated using cytofluorimetry for detection of cell-surface markers, reactive oxygen species (ROS) and phagocytosis.

Results

D-mannose decreased expression of MHCII molecule in dendritic cells and macrophages while expression of CD86, CD11b and CD11c remain unchanged. Phagocytosis was impaired in macrophages and dendritic cells after treatment with D-mannose. D-mannose did not influence on ROS production by macrophages.

Conclusion

These results indicate that D-mannose interferes with antigen presentation in dendritic cells and macrophages, thus suggesting tolerogenic effects of the compound. Further studies are needed to support this observation.

AUTO1-0568
IMMUNOMODULATION

SIMVASTATIN TREATMENT OF ALOPECIA AREATA

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Background

Alopecia areata (AA) is a T-cell-mediated autoimmune disorder involving the lymphocytic infiltration and destruction of the hair follicle during the active phase of hair growth, presenting with varying patterns of hair loss. Previously, we have shown that the cholesterol-lowering drugs simvastatin and ezetimibe restores total levels of T regulatory lymphocytes in a mouse model of AA.

Method

Following 3-month topical treatment with simvastatin or vehicle, lymph nodes were harvested and analyzed via flow cytometry and Western blotting. Mouse blood serum was also collected for lipid analysis. *In vitro* studies were performed on cytotoxic CTLL-2 cells and lymph node cells from mice with AA.

Results

Here we demonstrate that topical application of simvastatin to AA lesions induces remission in the CEH/HeH mouse model of AA. Among the mice who experienced hair re-growth with this treatment, complete re-growth was associated with decreased serum cholesterol levels characteristic of statin treatment, whereas cholesterol levels in treated mice with only partial or no re-growth was associated with no significant decrease in cholesterol. Analysis of skin-draining lymph nodes also indicated reduced levels of pSTAT1 and NKG2D in mice with complete hair re-growth. *In vitro* studies demonstrated an anti-proliferative effect of simvastatin on the cytotoxic T cell line CTLL-2 and primary C3H/HeH lymphocytes

Conclusion

These results suggest that simvastatin treatment reverses autoimmune hair loss through the direct modulation of T cell activity.

AUTO1-0201
IMMUNOMODULATION

SCYTONEMIN INHIBITS THE EXPRESSION OF INDUCIBLE NITRIC OXIDE SYNTHASE AND TUMOR NECROSIS FACTOR-ALPHA IN VITRO AND IN VIVO

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Background

Scytonemin, a pigment isolated from cyanobacteria, has been reported to exert a anti-inflammatory effect. In this study, we examined the effect of scytonemin on lipopolysaccharide (LPS)-induced production of inflammatory mediators, including nitric oxide (NO) and tumor necrosis factor-α (TNF-α), in macrophages and investigated the molecular mechanisms responsible for its effects.

Method

RAW 264.7 cells were stimulated by lipopolysaccharide in the presence and absence of scytonemin. NO production and TNF-α secretion in culture supernatants were analyzed by Griess assay and ELISA. The mRNA expression of iNOS and TNF-α was analyzed by quantitative RT-PCR. Western immunoblot assay was performed for analysis of intracellular signaling. Phorbor ester-induced skin inflammation was used for in vivo experiments.

Results

Scytonemin significantly inhibited NO production and inducible nitric oxide (iNOS) mRNA expression in LPS-stimulated macrophages. The secretion and mRNA expression of TNF-α was also suppressed by scytonemin treatment in RAW 264.7 cells. Further study demonstrated that scytonemin attenuated LPS-induced NF-κB/Rel activation in RAW 264.7 cells. In addition, scytonemin also suppressed phorbol ester-induced skin inflammation by blocking the expression of iNOS and TNF-α in BALB/c mice.

Conclusion

These results suggest that scytonemin inhibits the expression of inflammatory mediators, at least in part, by blocking NF-κB/Rel activity and might be a potential therapeutic agent for the treatment of inflammatory diseases.

AUTO1-0130
IMMUNOMODULATION

PERIOSTIN IS A KEY MOLECULE FOR DEVELOPMENT OF NASAL POLYPOSIS

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Background

Periostin has emerged as a novel mediator in chronic states of allergic diseases and plays a role in tissue remodeling in allergic inflammation. However, its role in nasal polyps remains unclear.

Method

Expressions of periostin and its receptor, integrin αV, were investigated. Immunohistochemistry and immunocytochemistry were used to determine cellular sources of periostin. The human mast cell line, LAD2 cells were stimulated with IgE, IL-4, IL-13 or TNF-α and periostin measured. Normal human bronchial epithelial cell (NHBE) was stimulated with periostin, IL-4, IL-13, TNF-α, and dsRNA alone or in combination and thymic stromal lymphopoietin (TSLP) measured in the culture supernatants.

Results

Periostin was up-regulated and positively correlated with IL-5, CCL-11 and CT scores in eosinophilic nasal polyp (E-NP), but not in non-eosinophilic NP. Tryptase (+) cells were a main source of periostin in E-NP. Periostin levels were also correlated positively with total IgE in E-NP homogenate. Furthermore, IgE stimulation enhanced the mRNA and protein levels of periostin. Confocal microscopic examination of LAD2 cells showed that periostin was localized in the granules. Overexpression of integrin αV was observed in E-NP and correlated positively with the levels of periostin in E-NP. Periostin and integrin αV expressions were positively associated with TSLP in E-NP. Treatment with periostin induced more TSLP production in NHBE than those without periostin, in combination with IL-13 or IL-4 and TNF-α or dsRNA.

Conclusion

Periostin is upregulated in E-NP and human mast cells may be a major source of NP-derived periostin, which may induce TSLP production from epithelial cells.

AUTO1-1002
IMMUNOMODULATION

PRIMARY PROPHYLAXIS FOR PNEUMOCYSTIS PNEUMONIA IN PATIENTS TREATED WITH IMMUNOSUPPRESSIVE/IMMUNOMODULATORY AGENTS: THE EXPERIENCE OF ONE CENTRE

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Background

Pneumocystis jirovecii pneumonia (PJP) can affect immunocompromised patients and may cause severe morbidity and mortality. This condition may be preventable by prophylactic antibiotics in high risk patients.

Method

We retrospectively review medical records of patients evaluated, between 2014 and 2017, at the “Infection risk screening apointment” - led by Infectious diseases Service – and specially dedicated to those starting immunosuppressive / immunomodulatory treatment.

Patient demographics, diagnosis, immunosuppressive treatment, and decision criteria for starting primary prophylaxis were analyzed.

Results

A total of 541 patients was evaluated during this period, 512 with autoimmune or inflammatory diseases.
Thirty-four patients initiated primary prophylaxis for PJP. Half of them were referred by Rheumatology and 32% from Neurology physicians. The majority (91%) have an autoimmune or inflammatory disease. The most frequent diagnosis was Rheumatoid Arthritis (20.6%), followed by Myasthenia Gravis (11.7%), Systemic Lupus Erythematosus (8.8%), and Demyelinating diseases (8.8%). Granulomatosis with polyangiitis was present in only one patient.
Most of patients (85.3%) were treated with Prednisolone (79.3% of which more than or equal to 20 mg during more than 2 weeks). Other commonly prescribed drugs were biologic agents (17.6%), azathioprine (35.3%) and methotrexate (29.4%). A combination of immunosuppressive therapies was frequent (70.6%).
Sulfamethoxazole/ Trimethoprim was prescribed in all patients except one that was treated with atovaquone (due to Sulfamethoxazole/ Trimethoprim allergic reaction).

Conclusion

Indications for PJP prophylaxis in patients treated with immunosuppressive agents remain unclear. However, advanced age, structural lung disease, prolonged systemic corticosteroid therapy at high dose, vasculitis induction therapy and immunosuppressive agents combination are important decision-making factors.

AUTO1-0726
IMMUNOMODULATION

SYSTEMATIC REVIEW AND META-ANALYSIS OF SUBCUTANEOUS IMMUNOGLOBULIN IN AUTOIMMUNE NEUROMUSCULAR DISEASES

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Background

Recent studies of immune-mediated neuromuscular diseases indicate that subcutaneous immunoglobulin (SCIG) may be an effective alternative to intravenous immunoglobulin (IVIG) by increasing patient adherence, independence and quality of life. This review aims to evaluate efficacy, safety, residual IgG, impact on quality of life and satisfaction of patients treated with SCIG in neuromuscular diseases.

Method

Potentially relevant studies (between January 2007 and April 2017), were identified with MEDLINE, EMBASE, EBSCO, Web of Science, Cochrane library. Main outcome was efficacy evaluation of SCIG by changes in clinical scales of overall muscle strength or muscular disability scale. Secondary outcome was safety evaluation, serum IgG residual, and satisfaction or quality of life. The I^2 statistic homogeneity assumption was used to evaluate heterogeneity.

Results

A total of 402 patients from 21 studies were reviewed in this meta-analysis. The mean difference for efficacy, IgG level and patient satisfaction or quality of life was respectively 0.77 (P = 0.19) (figure 1), 13.08 (P <0.52) and 9.18 (P <0.0001) (figure 2). Combined risk reduction for moderate or systemic side effects was 86% (RR = 0.14, 0.09-0.23) (figure3). The results indicate that weekly SCIG show clinical efficacy as good as IVIG, maintain a high level of serum IgG which remains constant and preventing systemic secondary effects.

Conclusion

SCIG is nowadays a therapeutic alternative in autoimmune neuromuscular diseases. It offer several advantages in terms of tolerance profile, satisfaction, quality of life. Several steps remain to be taken, notably to widen the knowledge on the therapeutic response of the SCIG.

AUTO1-0317
IMMUNOMODULATION

THE EFFECT OF ETHYL PYRUVATE ON REGULATORY T CELLS DURING TYPE 1 DIABETES DEVELOPMENT

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Background

Type 1 diabetes (T1D) develops as a consequence of pancreatic beta cell destruction mediated by various pro-inflammatory mediators. Since current T1D therapy mainly involves insulin replacement, constant efforts are being directed toward establishing novel therapeutic approaches. Ethyl pyruvate (EP) is a stable ester of pyruvate, key biochemical intermediate in carbohydrate metabolism. EP has shown anti-oxidant and anti-inflammatory activity in different disease models such as severe sepsis, acute respiratory distress syndrome, acute pancreatitis and stroke. The aim of this study was to evaluate the potential role of EP in T1D therapy.

Method

T1D was induced by multiple low doses of streptozotocin (MLDS) in male C57BL/6 mice and EP was administered intraperitoneally for 9 days (100 mg/kg bw) in a prophylactic manner (simultaneously with first streptozotocin) or in a therapeutic manner (one day after the last streptozotocin). *Ex vivo* flow cytometry analysis of Th1, Th2, Th17 and Treg subpopulations in spleen, pancreatic lymph nodes and mononuclear pancreatic infiltrates was performed.

Results

EP treatment significantly reduced T1D incidence in mice and preserved pancreatic islets when administered in prophylactic manner, while therapeutic EP treatment conferred transient protection from T1D development. The prophylactic EP treatment had no effect on the number or proportion of Th1, Th2 or Th17 cells. However, the number of T regulatory cells was significantly elevated within pancreatic lymph nodes and mononuclear pancreatic infiltrates.

Conclusion

Protective effect of EP on T1D development could be a result of enhanced *in situ* Treg proliferation or Treg migration to the pancreas.

AUTO1-0044
IMMUNOMODULATION

COMPARISON OF ANTI-INFLAMMATORY EFFECTS OF ALPHACALCIDOL OR PREDNISONE TREATMENT IN ACTIVE RHEUMATOID ARTHRITIS

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Background

The aim was to compare clinical and laboratory anti-inflammatory effects of alphacalcidol (1αD3) or prednisone (CS) treatment in patients with active Rheumatoid arthritis (RA).

Method

The study included 67 RA patients (pts) on methotrexate (MTX) therapy. Written consent, demographics and blood samples for ESR, CRP, 25(OH)D3, PTH, cholesterol (tC), HDL, LDL, calcium, IL6, IL4, IL10, TNFα measurement were obtained, 24h calciuria and disease activity (DAS28 score)calculated. Pts were randomly assigned to three-month treatment with 1μg (group A1), 2μg (group A2), 3μg (group A3) 1αD3 daily or CS (group C) 20 mg daily,one month and 10 mg afterwards. At the end of study treatment, disease activity and laboratory tests were reassessed.

Results

Out of 67 pts, 68,65% were females, MTX dose 15,41 ± 3,28 mg/w, RA activity - DAS28 5,58 ± 0,905. Pts were fully comparable. After three-month treatment, we found highly significantly reduced disease activity in all four treatment arms as per DAS28 (p<0,01, paired t-test). Comparison between the groups in term of Δ DAS28 (p<0,05, ANOVA) showed that the group A2 and C did not differ. Alphacalcidol 2μg treated patients (N=19) significantly reduced CRP (p<0,01), ESR, IL6 levels (p<0,05), significantly elevated HDL (p<0,05). Serum levels of 25(OH)D3 in CS users (N=16) significantly decreased (p<0,01, paired t-test). Urinary calcium significantly increased in 3μg 1αD3 treated pts (N=16), yet not exceeding ULN (p<0,01).

Conclusion

Treatment either with 1μg, 2μg, 3μg 1αD3 or prednisone for three months, produced significant reduction of disease activity. 1αD3 2μg daily showed equall clinical and biochemical anti-inflammatory effects as CS.

AUTO1-0388
IMMUNOMODULATION

ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES AS A MODEL SYSTEM TO STUDY THE ROLE OF GLIAL CELLS AND NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

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Background

Neurodegenerative diseases are characterized by the aggregation of misfolded proteins and concomitant inflammatory processes. A hallmark of AD are amyloid plaques in the patient's brain. Current evidence pinpoints towards a crucial role of inflammatory processes in the progression of the disease. In the central nervous system, non-neuronal (glial) cells including microglia, astrocytes, and oligodendrocytes act as regulators of inflammation. Upon activation, microglia shift from a resting to an active state accompanied by a change in the profile of released cytokines. Depending on the activating stimulus, microglia and astrocytes adopt either a neuroprotective or neurotoxic phenotype, making them an interesting target for therapeutic interventions. Oligodendrocytes are not involved in immune reactions, but react upon inflammatory cytokines released by microglia and astrocytes. In the present study we aim to investigate the possible impact of glial cells on amyloid-beta (Aβ)-induced neurotoxicity as well as on neuroinflammatory processes.

Method

As model system we utilized organotypic hippocampal slice cultures (OHSC) since the *in vivo* composition of all cell types present in the hippocampal region is represented. To address the question which impact glial cells exert on Aβ-induced neurotoxicity and inflammation, a pharmacological treatment is used to remove microglia from OHSC obtained from postnatal C57BL/6 mice (P1-4). Astrocytes and oligodendrocytes will be depleted using a toxin-coupled antibody-based approach. Additionally, we investigate inflammatory cytokines in response to Aβ.

Results

Conclusion

The aim of this project is to establish OHSCs as an adjustable model to study the role of distinct glial cells to understand pathological mechanisms underlying acute and chronic inflammation.

AUTO1-0550
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

POSSIBLE IMMUNOMODULATION OF RANTES SIGNALING PATHWAY BY HHV-6 IN PATIENT WITH AUTOIMMUNE THYROIDITIS

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Background

Human herpesvirus-6 (HHV-6) is widely distributed in the general population. The primary infection usually occurs in the early years of life and remains latent throughout the life.

HHV-6 is shown to contribute to several autoimmune disorders including autoimmune thyroiditis.

HHV-6 U12 and U51 genes encode putative homologues of cellular G-protein-coupled receptors (GCR) which have ability to bind RANTES. Expression of this genes in monocytes/macrophages (MO/Mϕ) showed to enhance productive HHV-6 infection by down-regulation of cellular chemokine RANTES.

Therefore, the aim of this study was to find out if these viral genes could influence RANTES expression in AIT patients.**Method**

In this study 40 (age range 32-67) AIT patients and 20 (age range 21-58) blood donors were enrolled. Peripheral blood mononuclear cells' DNA was tested on the presence of HHV-6 genomic sequence by nPCR. Total RNA isolated from patients and donors' PBMCs was used for detection of HHV-6 U12 and U51 mRNAs. RANTES level was identified by ELISA in peripheral blood plasma.

Results

Presence of HHV-6 genomic sequences was significantly higher ($p<0.05$) in AIT patients' than in donors PBMC DNA samples (53% vs. 10%). HHV-6 U12 and U51 mRNAs were found only in 14% of patients' RNA samples. However, RANTES level was noticeably lower in AIT patients' than in donors' plasma samples.

Conclusion

Lower levels of RANTES in AIT patients' peripheral blood plasma in comparison to control group could be explained by immunomodulation of HHV-6. Higher frequency rate of HHV-6 in AIT patients' PBMC as well indicate on the importance of it in AIT.

AUTO1-0611
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

GUT MICROBIOTA DISTURBANCES (BREATH TESTS) AND NAEVUS COUNTS IN PATIENTS WITH DYSIMMUNITY (EXCEPT CANCER) CONSULTING IN GASTROENTEROLOGY

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Background

High naevus counts have been associated with decreased immunity.[1]

Intestinal dysbioses is observed in patients with autoimmuny.

Naevus counts or results of breath tests (to evaluate dysbiose) may differ according to the type of dysimmunity, including chronic inflammation such as metabolic syndrome (MS).

Method

From January 2016, all patients consulting a private gastroenterologist were enrolled. Naevi of the right arm were counted as previously published.[1] Breath tests were performed with MX6 (Gazdetect®). Ethylacetate, SO2 and H2S were measured two hours after the intake of fructose.

Results

The study includes 1,309 patients.

Patients with psoriasis or MS present more frequently with high naevus counts than Hashimoto's Thyroiditis (HT), Herpes Simplex Virus (HSV) or Crohn's disease (CD) ($p<0.001$).

Ethylacetate levels are lower in CD than in HSV ($p<10^{-9}$) or MS ($p<10^{-7}$), and lower in MS than in HT ($p<0.001$) or psoriasis ($p<0.01$).

SO2 and H2S levels are lower in CD than in HT ($p<0.01$). See table 1.

Naevus counts are higher in patients with increased SO2 levels ($p<0.01$) and lower in patients with increased ethylacetate or H2S levels ($p<0.001$). See table 2.

Table 1: Comparison of breath tests results and naevus counts in patients with HSV, HT, MS, psoriasis or CD

Diseases (nb of patients)	% of patients with ≥7 naevi on right arm	Breath test Ethylacetate ppm	Breath test SO2 ppm	Breath test H2S ppm
Psoriasis (189)	15.9	4.9+/-4.4 µ	0.2+/-0.27 µ'	0.24+/-0.40
Metabolic syndrome (249)	15.7 *	3.9+/-3.2 # ;* ; µ	0.18+/-0.16	0.33+/-0.65
Hashimoto thyroiditis (310)	10.3 *	5.2+/-4.4 *	0.2+/-0.3 µ	0.4+/-0.65 *
HSV1/2 (337)	9.8	5.2+/-5.8 §	0.16+/-0.23	0.28+/-0.46
Crohn (66)	9.6	2.7+/-3.0 §; #	0.13+/-0.15 µ; µ'	0.19+/-0.40 *
p values (only when<0.01)	*<0.001	§<10^{-9} #<10^{-7} *<0.001 µ<0.01	µ and µ'<0.01	*<0.001

Table 2: Comparison of breath tests results according to naevus counts

Naevus counts (nb of patients)	Breath test Ethylacetate ppm	Breath test SO2 ppm	Breath test H2S ppm
≥7 naevi on right arm (158)	4.04+/-3.55	0.25+/-0.35	0.15+/-0.28
<7 naevi on right arm (1151)	5.25+/-5.8	0.17+/-0.2	0.28+/-0.4
p	<0.001	<0.01	<0.000 1

Conclusion

Naevus counts and breath tests results are different according to dysimmune diseases.

Breath test results are different according to naevus counts.

Entanglements between naevus counts, skin immunity and gut dysbioses should be further investigated.

1. Ribero S et al. Br J Dermatol. 2016 Feb;174(2):312-8

AUTO1-0506
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

LEISHMANIASIS AMONG PATIENTS WITH IMMUNE-RELATED DISEASE: A DESCRIPTIVE STUDY.

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Background

Leishmania is an uncommon parasitic infection with two main clinical presentations, visceral (VL) and cutaneous (CL). The former is a severe disease related with a poor prognosis and it's incidence is higher among immunosupressed patients. Our aim is to describe leishmania infections in a single center among patients with immune-related disease (IRD).

Method

We retrospectively reviewed all cases of leishmaniasis attended in our hospital between january 2002 and june 2017.

Results

We found 180 cases of leishmaniasis in the study period (patient's characteristics are summarized in table 1). Among those, 23 (12.7%) were patients with IRD: 9 (39.1%) cutaneous psoriasis, 5 (21.7%) rheumatoid arthritis, 3 (13.0%) psoriasic arthritis, 2 (8.7%) ankylosing spondylitis, 1 (4.3%) ulcerous colitis, 1 (4.3%) Behçet disease, 1 (4.3%) Sjögern syndrome, and 1 (4.3%) polimyalgia rheumatica. IRD patient's characteristics are summarized in table 2. We found that IRD patients were older than no IRD patients ($p<0.001$). VL was not more frequent among IRD patients compared with non HIV non IRD patients. Among patients with IRD we found that corticoid use, and lower leukocyte ($p=0.03$) and lymphocyte ($p<0.001$) count were associated with VL.

	Immune-related disease (n=23)	HIV infection (n=25)	Others (n=132)
Age (mean)	58.4 (SD14.4)	39.6 (SD 6.6)	45.6 (SD 22.9)
Sex (Male/Female)	15/8	23/2	77/54
Diabetes	2 (8.7%)	0	16 (12.1%)
Chronic renal disease	2 (8.7%)	0	2 (1.5%)
Corticoid use	6 (26.1%)	0	3 (2.3%)
Visceral leishmaniasis	3 (13.0%)	17 (68.0%)	8 (6.1%)
Leukocyte count (median)	6900 (1570-9200)	2500 (650-7100)	6960 (2000-23100)
Lymphocyte count (median)	2100 (350-2910)	800 (130-3000)	2600 (400-12300)
Neutrophil count (median)	3340 (1180-5300)	1500 (300-3700)	3810 (400-14600)
Recurrence	4 (17.4%)	5 (20.0%)	9 (6.8%)
Death	0	2 (8.0%)	0

	Visceral leishmaniasis (n=3)	Cutaneous leishmaniasis (n=20)	p
Age (mean)	55.3 (SD 11.7)	58.9 (SD 15.0)	ns
Sex (Male/Female)	2/1	13/7	ns
Rheumatoid arthritis	1 (33.3%)	4 (20.0%)	ns
Cutaneous psoriasis	0	9 (45.0%)	ns
Psoriasic arthritis	1 (33.3%)	2 (10.0%)	ns
Others	1 (33.3%)	5 (25.0%)	ns
Corticoid use	3 (100%)	3 (15.0%)	**0.02**
Cortidoid dose (mean)	7.5 (SD 2.5)	5 (SD 0)	ns
DMARD use	3 (100%)	7 (35.0%)	ns
Biologic use	0	7 (35.0%)	ns
Leukocyte count (median)	3120 (1570-6900)	7120 (5100-9200)	**0.03**
Lymphocyte count (median)	1080 (350-6900)	2710 (2040-2910)	**<0.001**
Neutrophil count (median)	1620 (1180-4700)	3480 (2100-5300)	ns
Recurrence	1 (33.3%)	3 (15%)	ns
Death	0	0	ns

Conclusion

Despite the limitations of the study, we could conclude that leishmaniasis is rare among IRD patients and the prevalence of VL does not differ from general population, so routine invasive test in order to rule out VL is not justified. Corticoid use and lower leukocyte and lymphocyte counts are associated with VL among IRD.

AUTO1-0625
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

INFECTIOUS ANTIBODIES REPERTOIRE IN RHEUMATOID ARTHRITIS

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Background

The incidence of infectious diseases in the RA ADAPTHERA study by ELISA antibody screening and the differences in infectious distribution in active or low active disease patients was explored.

Method

Sera from 88 naive RA patients out of the ADAPTHERA study cohort, disease duration < 6 months, were tested for antibody titers against: Herpes simplex virus 1&2 (HSV1+2, IgG & IgM) Helicobacter pylori (HP, IgA & IgG), Cytomegalovirus (CMV, IgG & IgM), Toxoplasma gondii (Toxo, IgG), Adenovirus (IgG & IgM), Epstein Barr virus (EBV, IgG & IgM), and Parvovirus B19 (P-B19, IgG) were determined by using NovaLisa® from NovaTec Immundiagnostica GmbH, GERMANY. Borrelia (IgG & IgM) titers were determined by *AESKULISA*® and confirmed by Western blot (*AESKUBLOTS*®) by AESKU.DIAGNOSTICS GmbH & Co. KG, GERMANY.

Results

82% RA patients were found to be positive for HSV1+2 IgG (2% IgM positive), 8% for Adenovirus (IgA), 77% (IgG), and 1% (IgM). 99% for EBV-IgG (no IgM positive). 53% (IgG), and 26% (IgM) for CMV. 38% for HP-IgG and 15% for IgA and 79% for P-B19-IgG (3% IgM). 6% for Borrelia-IgM and 14% for IgG. A slightly increase was found for EBV sera positivity (99% IgG), compared to the normal population.

Conclusion

Limited evidence exists regarding the impact of the disease activity on the susceptibility for infections, possibly due to the close association of RA disease activity and therapy dependent dosage of immunosuppressive treatment. Still, some infections may present memory contact, presenting an epiphenomenon. On the contrary, they might play an active role in RA pathophysiology.

AUTO1-0592
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

TRANSIENT INFECTIOUS CELIAC AUTOIMMUNTY

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Background

Celiac disease is unique as it is induced by a trigger (e.g. gluten) and resolves by excluding it from diet.
However, a lymphocytic gastroduodenitis may be associated with a transient shift of celiac autoimmunity…

Method

1st Case:
A 3 year old girl is sent for a (weak) positive celiac serology
Duodenal biopsy found a duodenitis with Helicobacter pylori without celiac disease stigma. She is put on triple therapy and monitored clinically and immunologically every 3 months. After 1 year of follow up, anti-transglutaminase, anti-deamidated gliadin and anti-endomysium IgA and IgG were all negative

2nd Case :
A 13 years boy , followed for 4 years in private for failure to thrive that would be due to celiac disease (positive IgA antitragnsglutaminase serology but <20 IU / ml).Previous endoscopies with duodenal-jejunal biopsy highlighted a partial villous atrophy without cryptic enlargement. Another histology is ordered and denotes a marked giardiasis, leading to a 3 course treatment by metronidazole.

Subsequent negativity of celiac serology and the absence of genetic HLA risk allow free diet

Results

Celiac disease (CD) can, by itself, induce lymphocytosis along the digestive tract; but duodenal lymphocytosis are more than 80% of cases due to other etiologies that gluten intolerance.
Diabetes is also a highly prevalent cause of such transient positive autoimmunity without true gluten intolerance

Most authors do not advocate gluten-free diet at first, but any confounding risk, ie.genetic, makes mandatory a regular monitoring

Conclusion

Enteric infections simulating celiac disease should rise the awareness of a possible transient celiac autoimmunity before considering a definite diagnosis

AUTO1-0233
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

FIBROMYALGIA: NEW ABOUT PATHOGENESIS AND TREATMENT

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Background

Fibromyalgia is known as a chronic muscle pain with concomitant mental and cognitive impairment. We have managed to establish the general patterns of fibromyalgia development and progression including mental, infectious and immunological components of fibromyalgia. Both the conducted study and the practical experience of managing patients with fibromyalgia demonstrate the relationship between sleep disorders, pain intensity, inflammatory damage of enthesis and reactions of immune hypersensitivity types 2 and 3.

Method

We examined 69 patients. The examination protocol included psychometric testing on pain and anxiety scales, EEG of night sleep, ultrasound examination of entesitis in the field of typical pain for fibromyalgia, study of the immune status, myositis-specific and antinuclear antibodies, circulating immune complexes, specific markers of a number of infections, needle electroneuromyography (ENMG).

Results

All examined had total absence or severe deficiency of deep stages of sleep and predominance of superficial stages, fragmentation of night sleep. The level of anxiety was correlated with the severity of sleep disorders and the level of pain. In ENMG predominantly weak changes in the "myopathic" type. Ultrasound examination revealed criteria for current or completed enthesitis in painful areas of the body. Immunological studies demonstrated slow type 2 and 3 hypersensitivity reactions, with the activation of B1 cells, without the production of known myositis-specific antibodies. The treatment was based on the results of the studies.

Conclusion

The conducted research and practical experience of managing patients have shown the relationship between sleep disorders, the presence of infectious-mediated tendonitis and immune type 2 and 3 hypersensitivity reactions in fibromyalgia.

AUTO1-0547
INFECTION AND AUTOIMMUNITY: MICROBIOME, INFECTOME AND INTERACTOME

PRESENCE OF HHV-6B GENOMIC SEQUENCE AND HHV-6 U83 mRNA IN AUTOIMMUNE THYROIDITIS PATIENTS' THYROID TISSUES SAMPLES

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Background

Human herpesvirus 6 (HHV-6) is a lymphtrophic virus, however HHV-6 can also be found in solid tissues.

Recent studies have shown possible involvement of HHV-6 in the development of autoimmune thyroiditis (AIT), as it possesses immunomodulating properties. HHV-6B U83 gene encodes a chemokine that functions as a chemoattractant for monocytes. As the HHV-6B is a dominant species in Latvian population, the aim of this study was to find out frequency of HHV-6B and U83 gene expression in AIT patients from Latvia.

Method

In this study were enrolled 15 AIT patients (median age 46; IQR 40-54) and 15 thyroid tissue samples from autopsied subjects without thyroid pathologies as a control (median age 57; IQR 50-63). HHV-6B specific polymerase chain reaction (PCR) was assessed to identify frequency of viral genomic sequence in thyroid gland tissues' DNA. Reverse transcription PCR was used to identify HHV-6 U83 gene expression.

Results

HHV-6B genomic sequence was found in 14 out of 15 (94%) patients and in 8 out of 15 (53%) controls' thyroid gland tissue DNA samples. HHV-6B U83 mRNA sequence was found in 3 out of 14 (21%) AIT patients' and in none of controls' RNA samples isolated from thyroid gland tissues.

Conclusion

Our data demonstrate a higher presence of HHV-6B genomic sequence and U83 mRNA in AIT patients' thyroid tissues samples in comparison to the control group. To make final conclusion about involvement of HHV-6 in the development of autoimmune thyroiditis (AIT) further investigation is needed.

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AUTO1-0061
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

AUTOIMMUNITY IN PATIENTS WITH PERIODIC FEVER SYNDROMES

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Background

The etiology of the majority of autoimmune diseases is unknown. Several abnormalities in the innate immune system such as TLR abnormalities in patients with SLE have been observed. It is possible that defects in the innate immune system underlie autoimmune diseases. To address this question I examined patients with periodic fever syndromes for evidence of autoimmunity.

Method

Patients seen at Dartmouth Hitchcock Medical Center between 2011 and 2017 with a periodic fever syndrome were subject to a chart review.

Results

32 patient's records were examined and 2 of the patients disease appeared to resolve without a diagnosis. Of the 30 remaining patients 10 had PFAPA, 4 had TRAPS, 11 had FMF and 5 had other disorders. Of the 10 with PFAPA 5 had serologic and clinical examination for autoimmunity. 1 patient had erythema nodosum none had serologic evidence of autoimmunity. Of the 11 with FMF 6 had an examination for autoimmunity . One had rheumatoid factor, 3 had Hashimoto's thyroiditis, 1 had a positive ANA and 1 had Crohn's. In the other category 4 had an examination for autoimmunity and none had findings. Lastly, 4 patients with TRAPS were all evaluated for autoimmunity and 1 had CREST, 1 had SLE and 1 had undifferentiated connective tissue disease

Conclusion

The rate of autoimmunity is elevated in some patients with PFS particularly FMF and TRAPS. Larger prospective studies are warranted to address this issue

AUTO1-1016
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

ALTERED EXPRESSION OF MIR-146A IN MYASTHENIA GRAVIS THYMUS: A MOLECULAR BRIDGE BETWEEN INNATE IMMUNITY AND AUTOIMMUNITY

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Background

Toll-like receptor (TLR)-mediated innate immune response is suspected to play a pivotal role in myasthenia gravis (MG), an autoimmune disorder affecting neuromuscular junction and mainly mediated by anti-acetylcholine receptor (AChR) autoantibodies. Growing evidence indicates that uncontrolled TLR activation and chronic inflammation orchestrate hyperplastic changes in the thymus of MG patients, significantly contributing to anti-AChR autoimmunity development and perpetuation. MiR-146a acts as a negative regulator of TLR-mediated pathways by targeting the NF-κB signaling transducers IRAK1 and TRAF6. In this study we investigated the possible miR-146a contribution to the intra-thymic MG pathogenesis.

Method

By qPCR, we assessed the expression of miR-146a, IRAK1 and TRAF6, and of c-REL, a putative miR-146a target gene, in hyperplastic MG and control thymuses.

Results

We found a significant miR-146a down-regulation, accompanied by IRAK1 and TRAF6 overexpression, in thymuses from MG patients, untreated or treated only with cholinesterase inhibitors before thymectomy, compared to controls. Of interest, in corticosteroids-treated MG patients intra-thymic miR-146a, IRAK1 and TRAF6 mRNA levels were comparable to those of normal thymuses, thus suggesting that miR-146a down-regulation may be restored by the immunosuppressive treatment. Similarly, mRNA levels of c-REL, a gene involved in germinal center (GC) reaction, were significantly higher in hyperplastic thymuses of corticosteroids-naïve MG compared to corticosteroids-treated MG patients and normal thymuses, thus supporting a relationship among miR-146a down-regulation, c-REL expression and GC formation.

Conclusion

Our overall data suggest a role for miR-146a as molecular factor linking TLR-mediated innate immunity to autoimmunity in hyperplastic MG thymus.
Work supported by the Italian Ministry of Health (Grant number: GR-2013-02358564).

AUTO1-0398
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

NEUTROPHIL ENVIRONMENT INFLUENCES PHAGOCYTOSIS RELATED GENES IN JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE)

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Background

Reduced apoptotic cell removal and increased Neutrophil Extracellular Traps due to dysregulated phagocytosis lead to autoantibody production in JSLE, a multisystem autoimmune disease. Interferon (IFN) expression plays a key role in the pathogenesis of JSLE.

On stratifying patients into 'IFN high' and 'IFN low' groups (dependent on the expression of specific IFN induced genes) we observed phagocytosis-related genes TLR2, FcγRIIIb and S100A9 were differentially expressed between these groups and healthy paediatric controls.

Understanding if these changes are intrinsic to disease or induced by the disease environment is essential for finding targets for treatment.

Method

Apoptotic supernatant was collected from $1.5x10^6$ neutrophils (cultured for 24 hrs at 37°C). Healthy paediatric control neutrophils were stimulated with either IFNa (10ng/ml), apoptotic supernatant (+/-5%PBMC) or media. Gene and protein expression following IFNa (RNA n=6; protein n=5) and apoptotic supernatant (RNA n=3, protein n=5) stimulation was measured with qPCR and flow cytometry, respectively.

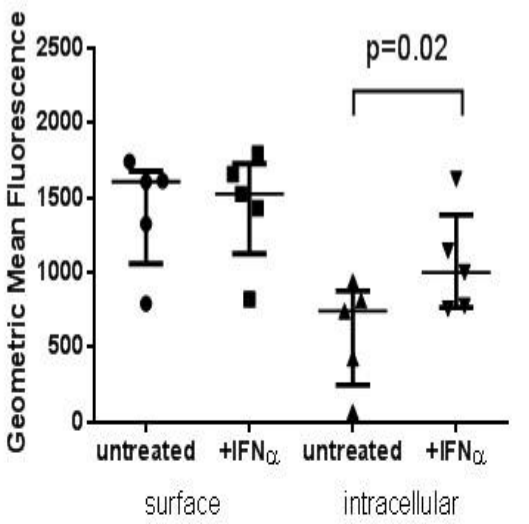
Results

No change was observed with TLR2 or S100A9 expression following incubation with IFNa. FcγRIIIb mRNA expression (mean±SEM) increased significantly in IFNa stimulated cells (0.11±0.018) compared to media (0.05±0.009; p=0.03). Intracellular FcγRIIIb protein increased significantly (p=0.02) while cell surface expression remained equal (Figure 1).

Intracellular S100A9 protein expression decreased with apoptotic supernatant stimulation while mRNA levels increased (preliminary data, Figure 2&3). TLR2 protein expression was unchanged, but incubation of apoptotic supernatant together with PBMCs indicated

an increase of mRNA.

1



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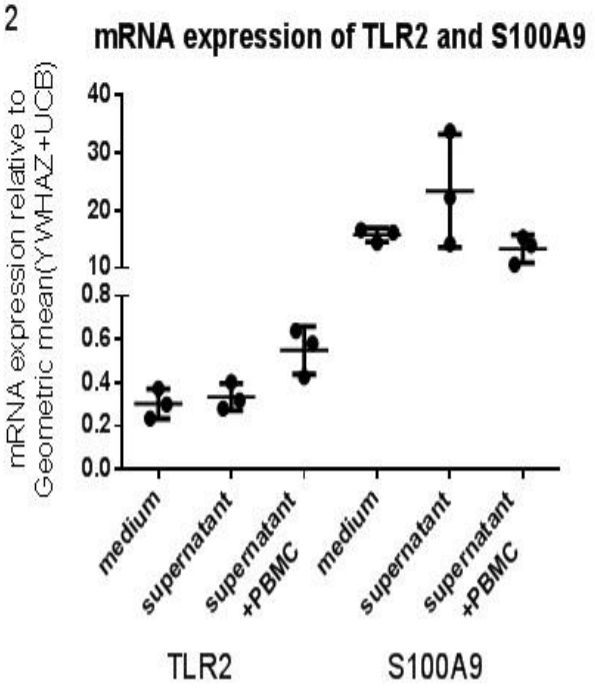
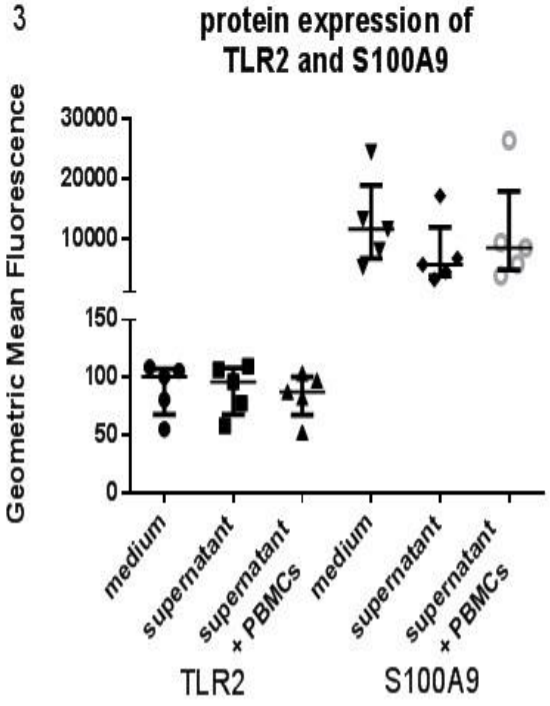


3



Conclusion

The neutrophil environment stimulates phagocytosis related genes, in particular the immune complex receptor FcγRIIIb. S100A9 may be released from cells stimulated with apoptotic supernatant.

AUTO1-0128
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

GLYCOGEN SYNTHASE KINASE 3B PROMOTES TLR3-MEDIATED ANTIVIRAL RESPONSE BY REGULATING C-SRC TYROSINE KINASE

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Background

Glycogen synthase kinase 3b (GSK3b) has been reported to regulate signal pathways for Toll-like receptor 3 (TLR3)-mediated inflammatory cytokine production. However, the mechanisms underlying GSK3b regulation of non-canonical TLR3-mediated antiviral response remain unclear.

Method

Results

Here we report that GSK3b positively regulates poly I:C-induced Src tyrosine kinase and antiviral gene expression. After poly I:C stimulation, GSK3b interacted with Src in a time-dependent manner. Furthermore, we found that the levels of Src phosphorylation and interferon (IFN) stimulated gene (ISG) expression were significantly reduced in the ablation or inhibition of GSK3b, while that levels were strongly elevated in the overexpression of GSK3b.

Conclusion

Together, our results suggest that GSK3b is critical for the poly I:C-induced non-canonical TLR3 signaling by regulating Src activation.

AUTO1-0653
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

PROBIOTIC LECTINS COMMUNICATE TO INNATE AUTOIMMUNITY

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Background

Probiotic lectins (PL: lactobacillary and bifidobacterial lectins, LL, LB) from ingredient strains of probiotics were established by us as systems recognizing different types of artificial polymeric glycoconjugates (GC) (www.lectinity.com). The aim was to evaluate the influence of different types of PL towards innate immunity protective cells.

Method

Influence of Acilact PL, bifidobacterial PL (strains *B.longum spp.adolescentis* MS-42*, B.bifidum No 1 and B.gallinarum GB, in equal protein proportions*) or GC on mice peritoneal macrophages was calculated as macrophage migration (MM) index. Human blood leukocytes TNF-alpha production was evaluated by ELISA. Agglutination titers of sialidase treated human A-group red cells by saPL and aPL were 2-8 mkg/ml.

Results

1.Stimulation of MM was observed as L-Fuc-PAA (14,5±1,3)>> Man-PAA(3,5±0,24)> GalNAc-PAA(1,0±0,08). **2.**In subhemagglutinating concentrations the influence of aLB(13,0±1,1), aLL(7,5±0,64) and saLL(7,0±0,52) on MM was similar to pseudofucan and less compared to pseudomannan/ pseudomucin action. The synergism of summary LL[sLL](13,0±01,6) influencing MM was observed. **3.** sLL induced production of TNF (420±32 pg/ml, spontaneous level 128±11, $P<0,05$) in contrast to saLL or aLL action (TNF 126-129 pg/ml) or action of phagocytosis of *B.bifidum* (TNF 134±41 pg/ml). sLL induced TNF in an opposite or distinct dose-dependent manner in comparison to LPS- or PHA-stimulation (TNF 320±36 and 234±19 pg/ml, respectively, $P<0,05$). Induction of leukocyte production of TNF needed subcytoagglutinating activities of PL combinations.

Conclusion

PL are involved in cross-talk “Biotope microbiocenoses—Innate immunity cell subpopulations” through mediation by GC as signals. It seems fucosylated GC play the special signal roles. The role of complex PL—GC relationships involving in mucosal innate autoimmunity is discussed.

AUTO1-0364
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

BENZOXAZOLE DERIVATIVES SUPPRESSED LIPOPOLYSACCHARIDE-INDUCED MAST CELL ACTIVATION

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Background

Mast cells are central regulators of allergic inflammation that function by releasing various proallergic inflammatory mediators, including histamine, eicosanoids, and proinflammatory cytokines. Occasionally, bacterial infections initiate or worsen allergic inflammation. Several studies have indicated that activation of lipoxygenase positive regulates allergic inflammatory responses by generating leukotrienes and proinflammatory cytokines.

Method

we have studied the effects of benzoxazole derivatives on lipopolysaccharide (LPS)-induced expression of proinflammatory cytokines, production of histamine, and surface expression of co-stimulatory molecules on bone marrow-derived mast cells (BMMCs).

Results

The benzoxazole derivatives significantly reduced expression of interleukin-1 beta, interleukin-6, interleukin-13, tumor necrosis factor-α, perilipin 2, and perilipin 3 in BMMCs treated with LPS. Furthermore, histamine production was suppressed in BMMCs treated with LPS, or non-adherent cells treated with phorbol-12-myristate-13-acetate/ionomycin. Benzoxazole derivatives marginally affected the surface expression of CD80 and CD86 on BMMCs in the presence of LPS, although LPS alone did not increase the expression of those proteins.

Conclusion

Benzoxazole derivatives downregulated proinflammatory reactions in mast cells, and might be potential candidates as anti-allergic agents to suppress mast cell activation.

AUTO1-0106
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

DYSREGULATED OSTEOCLASTOGENESIS IS RELATED TO NATURAL KILLER T CELL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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Background

To investigate the role played by NKT cells in osteoclastogenesis and their effects on inflammatory bone destruction.

Method

Patients with RA (n=25) and healthy controls (n=12) were enrolled in this study. *In vitro* osteoclastogenesis experiments were performed using peripheral blood mononuclear cells (PBMCs) in the presence of M-CSF and receptor activator of nuclear factor kB ligand (RANKL). PBMCs were cultured *in vitro* with α-galactosylceramide (αGalCer), and proliferation indices of NKT cells were estimated by flow cytometry. *In vivo* effects of αGalCer-stimulated NKT cells on inflammation and bone destruction were determined in collagen-induced arthritis (CIA) mice.

Results

In vitro osteoclastogenesis was found to be significantly inhibited by αGalCer in healthy controls, but not in RA patients. Proliferative responses of NKT cells and STAT-1 phosphorylation in monocytes in response to αGalCer were impaired in RA patients. Notably, αGalCer-stimulated NKT cells inhibited osteoclastogenesis mainly via interferon-γ production, in a cytokine-dependent manner (not by cell-cell contact), and down-regulated osteoclast-associated genes. αGalCer-treated mice showed less severe arthritis and reduced bone destruction. Moreover, proinflammatory cytokine expression in arthritic joints was found to be reduced by αGalCer treatment.

Conclusion

This study primarily demonstrates that αGalCer-stimulated NKT cells have a regulatory effect on osteoclastogenesis and a protective effect on inflammatory bone destruction. However, it also shows that these effects of αGalCer are diminished in RA patients, and that this is related to NKT cell dysfunction. These findings provide important information for those searching for novel therapeutic strategies to prevent bone destruction in RA.

AUTO1-0658
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

INNATE IMMUNITY GENE EXPRESSION SIGNATURE ASSOCIATED WITH DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that primarily affects joints. Although there is evidence about the contribution of innate immunity to RA pathogenesis, the information about the innate gene signature associated with RA and particularly disease activity is limited.

Method

To assess RA-associated gene expression signature of innate immunity genes in peripheral blood mononuclear cells (PBMC) and its relationship with disease activity as assessed by DAS28 score. We analyzed gene expression of *TLR1-10* and 19 members of *IL-1/IL-1* receptor family in PBMC from patients with RA (n=75) and age-matched healthy subjects (n=63) using high-throughput SmartChip Real-Time-qPCR system (WaferGen). Subgroups were formed based on the disease activity (non-active RA, n=39; active RA, n=36); DAS28 of ≥3.2 was taken as active RA. Statistics were performed using GenEx (Sweden).

Results

Comparative profiling revealed upregulation of *IL1RN*, *IL18*, *IL18R1*, *IL1RAP*, *SIGIRR*, *TLR3*, *TLR5* (P_{corr}<0.0003) in RA when compared to healthy controls. Upregulated expression of *TLR2*, *TLR4*, *TLR6*, *TLR8*, and downregulation of *TLR10* (*P*<0.04) was observed in active RA when compared to non-active patients. Disease activity positively correlated with expression of *TLR2*, *TLR4*, *TLR8* and negatively with *TLR10* (*P*=0.01). Interestingly, *TLR10* downregulation has not been reported in RA yet. Multivariate analysis revealed innate gene expression pattern associated with RA activity.

Conclusion

This study revealed innate immunity gene expression signature associated with disease activity in RA, typical by deregulation of *TLR2*, *TLR4*, *TLR8*, and *TLR10*. There is a potential use of the gene expression pattern for personalisation of RA treatment.

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AUTO1-0660
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

GENE EXPRESSION PROFILING REVEALED UPREGULATION OF INNATE IMMUNITY GENES IN ACTIVE LUPUS NEPHRITIS SLE PATIENTS

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Background

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Several studies on murine lupus suggested a role for TLR signaling and other innate immunity genes in LN pathogenesis, limited information exists in humans.

Method

The purpose of this study was to analyze gene expression of *TLR1-10* and 19 members of *IL-1/IL-1* receptor family in peripheral blood mononuclear cells from patients with SLE (n=75) and age-matched healthy subjects (n=38) using high-throughput SmartChip Real-Time-qPCR system (WaferGen). Subgroups were formed based on the biopsy-proven LN (with/without, 27/48) and disease activity renal-SLEDAI score (active LN, n=13; inactive LN, n=14). Statistics were performed using GenEx (Sweden).

Results

Comparative profiling revealed upregulation of *TLR4* and downregulation of *TLR10* (P_{corr}<0.02) in SLE when compared to healthy controls. Upregulated expression of *IL1RN*, *TLR2*, (*P*<0.007), *TLR1*, *TLR6*, *TLR8*, and *IL18* (*P*<0.04) was observed in active LN patients when compared to patients without LN and upregulated expression of *TLR1* and *TLR4* was observed between active LN and non-active LN patients (*P*<0.04). Multivariate analysis revealed innate gene expression pattern associated with LN.

Conclusion

This study revealed innate immunity gene expression signature associated with active LN in SLE patients. Our study further supports a putative role for innate immune mediators in the pathogenesis of LN and suggesting them as potential therapeutic target.

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AUTO1-0734
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

PROTEIN LEVELS AND AUTOANTIBODIES AGAINST LL37 AND IFI16 NUCLEIC ACID SENSORS IN PSORIATIC ARTHRITIS

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Background

The etiopathogenesis of psoriatic disease, including psoriasis and psoriatic arthritis (PsA), is still unclear, but recently it has been clarified why self-DNA become immunogenic in psoriatic disease, suggesting an important role of nucleic acid sensors such as LL37 and IFI16, in psoriatic disease. We aimed at investigating humoral and cellular response to LL37 and IFI16 in PsA.

Method

Serum samples from PsA patients and age- and sex-matched healthy controls (HC) have been tested for anti-LL37 (human synthetic LL37-based ELISA), IFI16 (capture ELISA) and anti-IFI16 (human recombinant IFI16-based ELISA). Confirmation of anti-IFI16 with protein radio-immunoprecipitation using marked 35S- K562 cell extract and Western blot.

Results

Anti-LL37 IgM antibodies were detected in 22/35 (63%) PsA sera, compared to 2/34 (6%) of HC ($p<0.001$). Two/22 (9%) anti-hLL37-positive subjects were in remission according to DAS28-CRP, compared to 5/13 (39%) anti-hLL37-negative patients ($p=0.036$). IFI16 was detected in 73/158 (46.2%) of PsA sera and correlated significantly with high levels of C reactive protein (50.7% vs 30.6%, $p=0.01$). Anti-IFI16 IgG was positive in 12% of PsA cases and correlated significantly with high levels of C reactive protein (63.2% vs 36.7%, $p=0.027$). Anti-IFI16 IgA was positive in 14.6% and were significantly increased in subjects with skin psoriasis (95.7% vs 77%, $p=0.045$). IFI16 was detected in 1/7 synovial fluid, while anti-IFI16 IgG antibodies in 3/7. IFI16 declined during anti-TNFalpha treatment.

Conclusion

Nucleic acid sensors LL37 and IFI16 elicit an adaptive immune response in PsA, and autoantibodies against LL37 and IFI16 correlate with disease activity.

AUTO1-0199
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

CLINICAL AND PARACLINICAL PROFILES ABOUT FREQUENT CASES OF AUTO-INFLAMMATORY DISEASES IN MOROCCO (FMF AND MKD)

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Background

Autoinflammatory syndromes are hereditary diseases caused by mutations ingenes involving the innate immunity, they have a common clinical profile ofrecurrent fevers intersected with irregulary intervals and a biological inflammation during crisis periods. From these diseases, Familial Mediterraneanfever (FMF), mevalonate kinase deficiency (MKD), are the most reported.

Method

In this study, we report eight cases with 4 of FMF and 4 others of MKD at A. Harouchi Children Hospital- Casablanca.

Results

Four girls were diagnosed and genetically confirmed FMF with an average age of 9 years (5-12 years) from consanguineous union, have fever associated with abdominal pain, arthralgia and arthritis, as well as rashes, present in 3 cases. MKD was diagnosed for three girls and one boy with an average age of 6.75 years (2-14 years). The main clinical presentation is represented by febrile periods during 2 to 3 days, separated by an asymptomatic interval. The diagnosis was first based on a evocative clinical profile associated with an increased excretion of urinary mevalonic acid in 3 cases and genetic test finding homozygous M694V mutation in 3 cases and heterozygous P369S mutation in 1 case of FMF, and V337I heterozygous mutation in one case of MKD . All patients had inflammatory biological syndrome.

Conclusion

Although their frequency, the prevalence of autoinflammatory diseases is still underestimated in Morocco, notably due to the rarity of reported cases or undiagnosed cases, the lack of availability of biological and genetic tests to the general public and the lack of financial resources for the establishment of the genetic study.

AUTO1-0937
INNATE AUTOIMMUNITY, TLRS AND AUTOIMMUNITY

DIRECT LPS RECOGNITION AND ACTIVATION OF CD8+T CELLS VIA TLR4 IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is an autoimmune disease characterized by abnormal immune responses to self-antigens.Toll-like Receptors (TLRs) have been established to recognize specific patterns of microbial components and lead to systemic immune responses in RA. TLRs are expressed by cells in inflamed joints of RA patients and variety of endogenous TLR ligands is present within those joints. This study suggests that the over expression of TLR4 in CD8+T cells from RA patients may contribute to the abnormal immune activation of pro inflammatory cytokines and enhance the acute inflammation.

Method

Clinical variations like disease duration, number of actively inflamed joints, number, and type of bones deformities, CRP, RF, Anti-CCP, ESR and therapeutic interventions were recorded for each patient and DAS 28 scores were calculated with the help of the clinician. We analyzed the expression of TLR4 in transcript level by real-time PCR and protein level by flow cytometry in CD8+T cells of RA patients. Different cytokines level was checked after stimulation of CD8+T cells in TLR4 agonist.

Results

A significant increased of TLR4 in patients with RA compared to healthy donors . We got a strong positive correlation between TLR4 expression and DAS 28 score. The ROC curve analysis confirmed the significance of TLR4 expression in RA patients . We found that TLR4 ligand responsiveness significantly increased the different inflammatory mediators in CD8+T cells of patients compared with healthy individuals after in vitro stimulation.

Conclusion

Our data suggest an increased expression of TLR4 in CD8+T cells play a major role in inflammation of RA patients.

AUTO1-0392
IVIG AND NATURAL AUTOANTIBODIES

ALZHEIMER'S DISEASE AND NATURALLY OCCURRING AUTOANTIBODIES - AN APPROACH FOR A PASSIVE IMMUNIZATION AGAINST NEURODEGENERATION

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Background

AD is characterized by the misfolding and extracellular deposition of the β-Amyloid (Aβ) peptide within the brain. Aβ accumulates to oligomers of different sizes and leads to neuronal cell death, expressed by i.a. cognitive impairment. In this context, naturally occurring autoantibodies against Aβ (nAbs-Aβ) are able to prevent peptide aggregation und its deposition on neurons by mediating the phagocytosis by microglial cells. As nAbs belong to the B1 cell pool of lymphocytes they are secreted into the body fluids constantly over the entire lifetime. B1 cells act T-cell independent and are of innate nature. However, AD patients show a significant decreased titer of nAbs-Aβ, which strengthen the importance of these nAbs for the maintenance of a healthy brain.

Method

At present IVIg is used for antibody based therapies and nAbs-Aβ could be enriched based on IVIg. But IVIg is a limited and cost-intensive product. We follow up an approach extracting nAbs-Aβ antigen binding sequences based on FACS single cell sorts of $A\beta^{+}$ B1 cells, followed by single cell RT-PCR and transfection of HEK293 cells with the antibody constructs to produce recombinant antibodies.

Results

Monoclonal antibodies produced that way will be enriched from cell culture supernatants and tested *in vitro* for binding and functional activity. The best Aβ clearing antibody will further be tested in an AD mice model.

Conclusion

Recombinant antibodies on the basis of nAbs-Aβ sequences are produced IVIg independent and under standardized conditions and could be used as therapeutic agent in the treatment of AD.

AUTO1-0545
IVIG AND NATURAL AUTOANTIBODIES

TEMPORAL ASSOCIATION BETWEEN INTRAVENOUS IMMUNOGLOBULIN ADMINISTRATION FOR RHEUMATIC DISORDERS AND THROMBOEMBOLIC EVENTS- A CASE SERIES AND REVIEW OF THE LITERATURE

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Background

The objectives of the study are to report the association between intravenous immunoglobulin(IVIg) treatment in patients with rheumatic diseases and thromboembolic events.
and to review the literature on the subject.

Method

The clinical presentation, course and outcome of thromboembolic events occurring post-immunoglobulin infusion in nine patients is described. literature was reviewied from 1996 to 2017.

Results

Nine patients had a thromboembolic event within a week after receiving an IVIg infusion. All patients except one were female ranging in age from 22 to 69 years.

Six of the patients had an arterial thrombosis, three patients sustained a venous thrombosis.
Two events occurred during the IVIg infusion, three within an hour after the last infusion, one event occurred few hours after the initiation of the therapy, another occurred 3 days after receiving the IVIg treatment course, two events, a week after the treatment course has ended.
55% of the patients had no thrombogenic risk factors.

30% of systemic sclerosis patients were treated with IVIg, the majority of which had no additional thrombotic risk factors, had sustained a thromboembolic event within a week of receiving the last dose. Most events occurred within an hour of the last infusion, and involved the arterial tree.

Conclusion

Thromboembolic events after IVIg infusions, although infrequent, may occur in relatively young patients, even in the absence of risk factors for thromboembolism. No relation was found between the number or the frequency of infusions, to the thromboembolic events.Heightened awareness of possible thromboembolic events, even in "low risk" patients, is encouraged for at least a week period following treatment.

AUTO1-0125
IVIG AND NATURAL AUTOANTIBODIES

CLINICAL-IMMUNOLOGICAL CORRELATION AND HLA ASSOCIATION OF SCLERODERMA ANTIBODIES

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Background

Systemic sclerosis (SSc) is a multisystem connective tissue disorder characterized by excessive fibrosis of skin and internal organs and microvascular damage. Autoimmunity is considered to be involved in the pathophysiology. Autoantibodies do not seem to be simply epiphenomena, but are involved in disease pathogenesis. The objectives of this work were to: (1)- correlate the profile of the following specific autoantibodies with clinical and laboratory manifestations; (2)- investigate HLA class II associations with systemic sclerosis (SSc).

Method

We searched the database pubmed for studies that reported autoantibodies scleroderma and HLA association in all over the world. The search was conducted based on specific Medical Subject Headings (MeSH) and keywords. All languages were searched initially, but only English language studies were selected.

Results

It is believed that the SSc-specific autoantibodies are responsible both for amplifying immune response and targeting cell types that are relevant in the pathophysiology of SSc. Many ANAs are specific for SSc, including antibodies against topoisomerase I (Scl 70), centromeres, RNA polymerase III (RNAP III).
There is an association with certain class II antigens of the major histocompatibility complex (MHC), including HLA-DR1, DR2, DR3, D5 and DR25. Multiple alleles of the Human leukocyte antigen (HLA) DRB1 have been also strongly associated with systemic sclerosis (SSc) and its clinical or serological subsets.

Conclusion

The clinical subtype of the disease and some clinical manifestations in SSc may correlate positively with the presence of specific autoantibodies. These data indicate unique and multipleHLA-class II effects in SSc, especially on autoantibodymarkers of different subphenotypes.

AUTO1-0287
IVIG AND NATURAL AUTOANTIBODIES

Fully human monoclonal antibodies to Phosphorylcholine (PC) improves phagocytosis efficiency and reduces inflammation in ex-vivo cell culture model

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Background

Dual role of natural IgM antibodies (Nabs) in assisting the clearance of apoptotic cells and reducing atherosclerotic plaques size has been suggested previously. We developed a panel of fully human monoclonal IgG1 antibodies against phosphorylcholine, PC (A01, D05 and E01), from healthy human-donors via single-cell sorting of PC-reactive B-cells and consequent cloning/production in human embryonic kidney (HEK) cell system.

Method

TAMRA labeled apoptotic Jurkat cells were fed to PBMC derived M2 macrophage with or without anti-PC IgG1's (A01, D05, E01 or isotype control) prior incubation. Phagocytosis efficiency was assessed by number of macrophages up-taking TAMRA labeled Jurkat cells to the total number of macrophages in the given area. Additionally anti-inflammatory property of these antibodies was tested in LPS induced THP1 macrophages upon prior incubation.

Results

Among the three anti-PC clones, D05, improves phagocytosis efficiency by 53%(p=0,007) from 25%(in normal M2 macrophages) followed by E01- 37%(p=0,05) and then A01-28% (p=NS).

Similarly, we observed clone D05 significantly reduced the LPS induced inflammation in THP1 derived macrophages (p=0,002).

Conclusion

The impaired clearance of apoptotic cells and inflammation are the hallmark feature in both SLE and formation of necrotic core in atherosclerosis. The dual efficiency of these antibodies could effectively improves clearing the dead cell while simultaneously reducing the inflammation in SLE patients, although, molecular mechanism underlying deserves further study.

AUTO1-0342
LIVER AND AUTOIMMUNITY

UTILITY OF NOVEL AND CLASSICAL LIVER MARKERS IN THE DIAGNOSIS OF AUTOIMMUNE LIVER DISEASES

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Background

Primary biliary cholangitis (PBC) is characterized by the presence of anti-mitochondrial antibodies (AMA). While >90% of patients have AMA IgG, at least 5-10% of patients with clinically-proven PBC are seronegative for AMA. Recently two novel proteins kelch-like 12 (KLHL12) and Hexokinase 1 (HK-1) have been described as antibody targets in some seronegative, as well as in some seropositive PBC patients. The aim of this study was to evaluate these two novel markers along with fully automated AMA detection methods in a Spanish cohort.

Method The study included 92 samples from patients with PBC (n=21), autoimmune hepatitis (AIH, n=17), and disease controls (n=54). Samples were tested by ELISA for antibodies to KLHL12 peptide (KL-p) and HK-1 [research use only, Inova Diagnostics, USA] and by chemiluminescent immunoassays (CIA), QUANTA Flash M2 (MIT3) (Inova Diagnostics, USA) and ZENIT RA M2 (A. Menarini Diagnostics, Italy).

Results

The M2 CIAs demonstrated similar clinical performance and were also in high agreement (total agreement=94.6%, Cohen's *kappa*=0.84). Anti-HK-1 and KL-p antibodies were detected in 57.1% (12/21) and in 33.3% (7/21) of the PBC patients, respectively (see table). Of the 5 specimens negative for AMA by QUANTA Flash M2, 2 were dual positive for anti-KL-p and anti-HK-1 and 2 were positive for anti-KL-p only.

Performance Characteristic	QUANTA Flash M2 (MIT3)	ZENIT RA M2	HK-1	KL-p
Sensitivity in PBC (95% CI)	76.2% (54.9-89.4%)	76.2% (54.9-89.4%)	57.1% (36.5-75.5%)	33.3% (17.2-54.6%)
Specificity (95% CI)	95.8% (88.3-98.6)	94.4% (86.4-97.8)	90.1% (81.0-95.1%)	94.4% (86.4-97.8%)
Likelihood Ratio (+)	18.0 (6.2-57.3)	13.5 (5.4-35.2)	5.8 (2.7-12.6)	5.9 (2.0-17.3)
Likelihood Ratio (-)	0.25 (0.11-0.47)	0.25 (0.11-0.48)	0.48 (0.27-0.71)	0.71 (0.48-0.89)
Odds Ratio (OR)	72.5 (16.2-320.4)	53.6 (13.2-217.1)	12.2 (3.9-38.6)	8.4 (2.3-30.9)
Area Under the Curve (AUC)	0.94	0.92	0.81	0.76

Conclusion

Both automated detection methods for AMA demonstrated good clinical performance and inter-method concordance. The two novel markers demonstrated potential diagnostic utility for PBC in this cohort. Our data are in line with previous studies on anti-KL-p and anti-HK1 antibodies in PBC and specifically in AMA neg PBC.

AUTO1-0711
LIVER AND AUTOIMMUNITY

AUTOIMMUNE LIVER DISEASE-SPECIFIC AUTOANTIBODIES IN PATIENTS WITH CHRONIC VIRAL HEPATITIDES

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Background

Autantibodies related to autoimmune hepatitis type11 and type-2, and primary biliary cholangitis(PBC), detectable my indirect immunofluorescence(IF) or molecular based assays, are found in the great majority of the patients but <10% of patients without liver diseases or normal controls. The aim of the present study was to use antigen-specific assays to assess the prevalence of these autoantibodies in patients with chronic viral hepatitides B or C, as some studies report the presence of such autoantibodies in a considerable number of patients.

Method

Two hundred patients with viral hepatitis (100 with chronic hepatitis B and 100 with chronic hepatitis C) were tested for PBC-specific AMA (anti-M2, anti-M2/BPO), PBC-specific ANA (anti-sp100, anti-gp210, anti-NUP62) and AIH-2-specific anti-LKM1 (anti-CYPD6), anti-LC1 (FTCD) and anti-SLA (SepSecs) by in house ELISAs.

Results

PBC-specific anti-M2 AMA and anti-M2/BPO were found in 0 (0%) and 0 (%) patients with chronic viral hepatitis B and 0 (0%) and 3 (3%, 2 at very low titres, 1 in low) patients with chronic viral hepatitis C, respectively. PBC-specific nuclear anti-sp100, anti-gp210 and anti-Nup62 antibodies were found in 0(%), 0(0%) and 6(6%) patients with viral hepatitis B, and 1 (%), 1(%), and 5 (5%) patients with viral hepatitis C, respectively. AIH specific anti-SepSecs, anti-CYP2D6 and anti-FTCD antibodies were absent in all patients with viral hepatitides.

Conclusion

Molecular based assays show a specificity of at least 94% for autoimmune liver disease-related autoantibodies, supporting to a great extent the notion that such serological markers are highly specific for AIH and PBC.

AUTO1-0518
LIVER AND AUTOIMMUNITY

DIAGNOSIS OF AN OVERLAP SYNDROME OF AUTOIMMUNE HEPATITIS

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Background

Some patients present overlapping features between autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis. There is lack of consensus regarding clinical features: are the manifestations transition stages of one disease or represent two diseases in the same patient?

Method

The authors present a clinical report of an overlap syndrome.

Results

A 73-years-old woman was referred to our hospital due to an elevation in serum aminotransferase activity (SAA). She referred fatigue and abdominal pain. Physical examination revealed hepatomegaly and jaundice. Laboratory evaluation evidenced a normochromic normocytic anemia, an 8 fold increase in SAA, a slight elevation of alkaline phosphatase activity, an 8 fold increase in direct bilirubin, and a 2 fold elevation in IgG. The patient presented antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA) (++), and anti-mithocondria antibody (AMA) (+++) with anti-pyruvate dehydrogenase complex antibody of 28.6 U/ml (reference value <5 U/ml). Liver biopsy showed histological findings of interface hepatitis, portal plasma cell infiltrate and florid bile duct lesion.

Conclusion

The patient is a typical type 1 AIH: she presents ANA and SMA, an increase in SAA and in IgG, and has typical liver histological alterations. However, she has 73 years-old, suffers from fatigue, presents biochemical signs of cholestasis, has elevation of the SAA since 6 months, has AMA and presents histological characteristics of PBC. Altogether, the findings suggest the diagnosis of AIH-PBC overlap. Since cholestasis influence the response to immunosuppressive therapy, the identification of the overlap syndrome is important to establish an adequate therapeutic strategy.

AUTO1-0010
LIVER AND AUTOIMMUNITY

A PATIENT WITH AUTOIMMUNE HEPATITIS, MILD PANCREATITIS AND HYPERKINETIC DISORDER TREATMENT

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Background

We report a case of an 24 years old Slovenian caucasian male with asymptomatic pancreatic hyperenzymemia, increased IgG4 level and characteristic changes for autoimmune hepatitis(AIH). Jaudince, elevation of liver enzymes, anti smooth muscle antibodies and antinuclear antibodies were present. Since pancreatic hyperenzymemia is usually not seen in patients with manifestation of AH, we investigated hepatic and pancreatic histology. As an adolescent he began treatment of attention-deficit/hyperactivity disorder(ADHD) with methylfenidate and atomoxetine.

Method

An ultrasound-guided liver biopsy showed changes associated with autoimmune hepatitis: interface hepatitis, lobular hepatitis and marked plasma cell infiltration. Endoscopic ultrasound (EUS)-guided fine needle aspiration(FNA) of pancreatic tissue was performed for the evaluation of autoimmune pancreatitis. It was confirmed based on the presence of lymphoplasmacytic sclerosing pancreatitis and immunoglobulin IgG4 positive plasma cells in the infiltrate. For the definitive diagnosis, we used the Fukuoka 2010 International Consensus Diagnostic Criteria.

Results

We started steroid with satisfactory response on liver enzymes, jaundice and pancreatic hyperenzymemia and stop with atomoxetine therapy. For maintenance therapy we succsessfuly convert steroids to azathioprin in maximal dose daily. To get best patient therapy compliance and behavior changing, our patient underwent psychoanalysis to learn more about behavioral therapie.

Conclusion

We concluded that there might exist an overlap syndrome between Type 1 AIH and AP which was induced or exacerbated by long lasting hyperkinetic disorder treatment with combination of two drugs. Published evidence of liver and pancreatic adverse events of the off-label use of stimulant and nonstimulant combination therapy is very limited because of the small number of publications.

AUTO1-0731
LIVER AND AUTOIMMUNITY

ANTI-ASGPR AND ANTI-FILAMENTOUS ACTIN ASSIST SEROLOGICAL TESTING OF SUSPECTED AUTOIMMUNE HEPATITIS TYPE 1 PATIENTS

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Background

Since autoimmune hepatitis type 1 (AIH-1) serological hallmark ANA are not directed against a specific antigen [in contrast to AIH-1-specific SMA which target filamentous actin (F-actin)], a profile assay able to detect most ANA and SMA antigens in patients with suspected AIH-1 cannot be developed to replace indirect immunofluorescence (IF). ASGP-R antibodies are highly prevalent in patients with autoimmune hepatitis type 1 (AIH-1) but are also present in other autoimmune liver diseases making difficult to justify their urgent need.

Aim: To assess the prevalence of ASGPR in patients with AIH-1 in relation to Factin autoantibody reactivity by ELISA and to investigate whether ASGP-R can be an alternative target to complement AIH-1 serological testing

Method

Eighty AIH-1 patients (all SMA and/or SMA positive) were tested for ASGP-R and anti-F-actin antibodies by ELISA.

Results

Overall, 54 (67.5%) patients were positive for anti-F-actin and 25 (31.25%) for ASGP-R antibodies including 39 with anti-Factin only (48.8%), 9 with ASGPR only (11.2%)and 16 with double ASGP-R/F-actin antibodies. (20%) In double positive cases, no correlation was found between ASGP-R and anti-F-actin antibody titres. However, ASGPR antibodies were higher in patients with con-current anti-F-actin compared to anti-ASGP-R positive without anti-F-actin antibodies.

Conclusion

Anti-ASGP-R antibodies can be the only antigen-specific antibody reactivity in a significant percentage of patients with AIH-1 and their presence in profile tests may help the serological confirmation of suspected AIH-1 cases.

AUTO1-0613
LIVER AND AUTOIMMUNITY

AUTOANTIBODIES BY LINE IMMUNOASSAY IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background

The aim of this study is to determine the sensitivity of line immunoassay for the detection of serological markers of primary biliary cholangitis (PBC).

Method

Fifty-three PBC patients (45 woman, 8 men, median age 53 years 2 months) were studied. Sera were collected between 2013 and 2017 from 3 hospitals in the center of Tunisia. The inclusion criteria was the positivity of anti-mitochondrial antibodies (AMA) by indirect immunofluorescence. A line immunoassay was used to determine antibodies to AMA-M2, M2-3E (BPO), Sp100, gp210 and PML.

Results

The frequency of anti-AMA-M2, anti-M2-E3, anti-Sp100 and anti-gp210 was 96.2%, 100%, 28.3% and 34% respectively. Only one patient had anti-PML. Twenty-eight out of 53 patients (52.8%) had anti-Sp100 and/or anti-gp210. Only five patients out of 53 (9.4%) had both anti-Sp100 and anti-gp210.Ten patients out of 53 (18.9%) had anti-Sp100 but not anti-gp210 and Thirteen patients out of 53 (24.5%) had anti-gp210 but not anti-Sp100. In all PBC patients and in female patients, the frequency of anti-Sp100 was significantly lower than that of the combination anti-Sp100-anti-gp210 (28.3% vs 52.8%, p = 0.01 and 24.4% vs 53.3%, p=0.005 respectively). The frequency of anti-gp210 was lower than that of the combination anti-Sp100-anti-gp210 but reaching a borderline significance (34% vs 52.8%, p = 0.05).

Conclusion

The combination anti-Sp100-anti-gp210 increases the sensitivity of these tests from 28.3% and 34% respectively to 52.8%.

AUTO1-0752
LIVER AND AUTOIMMUNITY

SAFETEY AND EFFICACY OF DIRECT-ACTING ANTIVIRAL AGENTS FOR THE TREATMENT OF HCV IN RHEUMATIC DISEASES: CASE SERIES

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Background

Recent advances in antiviral therapy had completely modified the HCV infection approach. Direct acting antiviral agents(DAAs) are more efficacious, safer and more tolerable of IFN-HCV treatment.
Objectives: To show safety and efficacy of IFN-free HCV eradication in inflammatory arthritis patients with concomitantimmunosuppressive treatment.

Method

We evaluated 7 patients (M:F=5:2; median age 50.85±11.34), affected by inflammatory arthritis and concomitant HCVinfection treated with cDMARDs or bDMARDs and DAAs. Demographic data are showed in table 1.

Results

Pt 1 and 2 were affected by Psoriatic Arthritis with severe cutaneous and articular involvement. The first one was also under Lamivudina treatment because concomitant HBV infection and cirrhosis. Pt 3 was affected by enteropathic arthritis (RCU), treated with AZA 100 mg. Pt 4 was affected by rheumatoid arthritis and latent TBC under Nicizina 300 mg dailytreatment. Pt 5 was affected by ankylosing spondylitis. Before starting DAAs he was treated with Telaprevir/Peg-IFN/RBV but during the treatment vulgar psoriasis with diffuse and severe involvement appeared. IFN-therapy was interrupted and DAAs therapy started with no adverse events. Pt 6 was affected by ankylosing spondylitis and had concomitant HBV infection in prophylactic therapy with Entecavir. Pt 7 was affected by rheumatoid arthritis and cryoglobulinemic vasculitis. Five patients (1,2,4,5,6) were under anti-TNF-α treatment and 2 patient (3,7) was under cDMARDs treatment.

PTS	Age	Dgn	Concomitant Epatopaty	cDMARD bDMARD	DAAs	HCV Titre Pre-DAAS	HCV Titre Post-DAAS	Durati on T.	AE
01	62	PsA	HBV, cirrosi	IFX	Ribavirina Declastavir Sofosbuvir	2110126	<12	6	0
02	52	PsA	0	ADA	Ribavirina Sofosbuvir	2235436	<12	3	0
03	51	AR	HBV	AZA	Desabuvir Ombitasvir Paritaprevir Ritonavir	7034701	<12	3	0
04	46	AR	0	ETA	Ribavirina Sofosbuvir	2633651	<12	3	0
05	36	AS	0	ETA	Ribavirina Desabuvir Ombitasvir Paritaprevir Ritonavir	2168665	<12	3	0
06	53	AS	HBV	ETA	Ribavirina Declastavir Sofosbuvir	142984	<12	3	0
07	56	AR	Cirrosi	MTX+PDN	Ribavirina Simeprevir Sofosbuvir	510912	<12	6	0

Conclusion

For all of patients IFN-free therapy was efficacious (blood-HCV-RNA undetectable after treatment) and safe (noadverse events). DAAs therapy could be the best choice to HCV eradication in patients affected by autoimmune rheumatic diseasestreated with immunosuppressive drugs.

AUTO1-0593
LIVER AND AUTOIMMUNITY

ALLOIMMUNE NEONATAL HEMOCHROMATOSIS

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Background

Neonatal alloimmune hemochromatosis is the most common cause of neonatal liver failure and the leading indication for liver transplantation in infants, characterized by progressive iron deposition

We present two instructive case reports with favorable outcome

Method

First case :
A 45 days girl presents pallor, fatigue and failure to thrive, laboratory tests reveal acute hepatitis with liver failure. Alpha -fetoprotein is 64,000 IU and ferritinemia > 2000 ng/ml. The most likely diagnosis, neonatal hemochromatosis, required to initiate combination therapy with vitamin E and N- acetylcysteine. After 2 months, there are no more stigmata of liver failure.
Second case :
An 1,600-g female infant is delivered at 37 weeks' gestational age by a 30-year-old primiparous mother by emergency cesarean section for preeclampsia. The infant has correct Apgar scores and was well till day 10 when she presents anemia, jaundice and hypotonia along with moderate coagulopathy. She recovered progressively after 15 days of vitamin E with N- acetylcysteine and supportive therapy

Results

Neonatal hemochromatosis is the most common cause of neonatal liver failure , largely caused by gestational alloimmune liver disease , recognized to be a congenital alloimmune hepatitis and is defined as the association of severe neonatal liver disease with extrahepatic siderosis.
Other causes of NH encompass perinatal infection, trisomy 21, metabolic disorders and inborn errors of metabolism, and severa peculiar syndromes
Such diagnosis has prompt implications for future pregnancies, as current guidelines support the use of IVIG

Conclusion

Hepatic failure in a newborn infant should raise the suspicion of alloimmune hemochromatosis and guide neonatal managmenet and pregnancies prophylaxis

AUTO1-0567
LIVER AND AUTOIMMUNITY

ANTI-RODS AND RINGS AUTOANTIBODIES IN HEPATITIS C PATIENTS TREATED WITH INTERFERON-FREE SCHEDULES

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Background

The anti-Rods and Rings antibodies (anti-RR) are thought to occur in the context of therapy with drugs interfering with cytidine and guanosine triphosphate synthetic pathway. Anti-RR act against “rods and rings” structures (RR), mainly consisting from inosine monophosphate dehydrogenase-2 (IMPDH2). Anti-RR are observed in HCV patients treated with interferon (IFN) with ribavirin (RBV) (20-38%) but its role in chronic liver disease and efficacy of antiviral therapy remains unclear. Its potential role as a marker of a drug-induced autoimmune reaction is still a matter of researchers debate.

Method

Anti-RR were investigated by indirect immunofluorescence using HEp-2 cell substrate (Mosaic Basic Profil 1®, EUROIMMUNE, Lubeck, Germany) in chronic hepatitis C genotype 1 patients treated with ombitasvir/paritaprevir/r and dasabuvir (3D) +/-RBV before and after therapy.

Results

Anti-RR antibodies were found in sera of 4 patients (Table 1). In two-year follow-up anti-RR are still detectable. All patients achieved sustained viral response.

Pt.	sex/age	treatment history	IFN-free schedule	anti-RR first detection
1	F/54	PEG-IFN/ RBV	3D	12 weeks of follow-up
2	M/34	IFN	3D/RBV	24 weeks of follow-up
3	F/66	naive	3D/RBV	24 weeks of follow up
4	F/70	PEG-INF/RBV	3D	from baseline with increased titre at follow-up

Table 1. Patient characteristics

Conclusion

1. Anti-RR are found in hepatitis C patients after interferon-free therapy and are still detectable at 2 years follow up.
2. Anti-RR does not affect response to hepatitis C interferon-free therapy

Clinical relevance of anti-RR needs further investigations.

AUTO1-0704
LIVER AND AUTOIMMUNITY

EVALUATION OF A NOVEL MULTI-ANALYTE ASSAY FOR THE DETECTION OF AUTOANTIBODIES IN THE DIAGNOSIS OF PRIMARY BILIARY CHOLANGITIS

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Background

Primary biliary cholangitis (PBC) is characterized by the presence of anti-mitochondrial antibodies (AMA). While >90% of patients have AMA IgG, at least 5-10% of patients with clinically-proven PBC are seronegative for AMA. Besides the classical, other autoantibodies including those directed against hexokinase 1 (HK-1) and Kelch-like 12 peptide (KL-p) can be used as an aid in the diagnosis of PBC. This study aimed to analyze the clinical performance of a new fully automated bead-based assay for the detection of autoantibodies to classic and novel PBC antigens using clinically characterized PBC patient samples and controls.

Method

A total of 399 patient samples from the SIPMeL multi-center cohort (Italy) were analyzed. Of these, 194 were PBC patients, 69 were autoimmune hepatitis (AIH), 61 were from various other liver conditions and controls, and 75 had an unconfirmed diagnosis. Of the 194 PBC patients, 68 were considered AMA-negative by lab testing at each site. Samples were tested for antibodies to MIT3, HK-1, sp100, gp210, and KL-p using a novel fully automated bead-based immunoassay (research use only, Inova Diagnostics, USA).

Results

The sensitivity and specificity for all PBC autoantibodies are outlined in the table below. MIT3 alone detected 89.7% of AMA+ specimens with 96.9% disease specificity. Using a combination of MIT3, gp210, sp100, HK-1 and KL-p, 63.4% (46/68) of the AMA-negative PBC patients were detected.

Performance Characteristic	MIT3	gp210	sp100	HK-1	KLHL12
Sensitivity in PBC (AMA+ and AMA -) (95% CI)	63.4% (56.4-69.9%)	19.6% (14.6-25.7%)	26.3% (20.6-32.9%)	48.5% (41.5-55.4%)	19.6% (14.6-25.7%)
Sensitivity in PBC (AMA+ only) (95% CI)	89.7% (83.1-93.9%)	15.9% (10.5-23.2%)	24.6% (17.9-32.8%)	57.9% (49.2-66.2%)	23.0% (16.5-31.1%)
Sensitivity in PBC (AMA- only) (95% CI)	14.7% (8.2-25.0%)	26.5% (17.4-38.0%)	29.4% (19.9-41.1%)	30.9% (21.2-42.6%)	13.2% (7.1-23.3%)
Specificity (95% CI)	96.9% (92.4-98.8%)	93.8% (88.3-96.8%)	88.5% (81.8-92.9%)	73.8% (65.7-80.6%)	98.5% (94.6-99.6%)
Likelihood ratio + (95% CI)	20.6 (8.2-530%)	3.2 (1.6-6.6)	2.3 (1.4-3.9)	1.9 (1.4-2.6)	12.7 (3.5-47.4)
Likelihood ratio - (95% CI)	0.38 (0.31-0.45)	0.9 (0.8-0.9)	0.8 (0.8-0.9)	0.7 (0.6-0.8)	0.8 (0.8-0.9)
Odds ratio (95% CI)	54.6	3.7 (1.7-8.1)	2.7 (1.5-5.1)	2.7 (1.6-4.3)	15.6 (4.1-59.6)

Conclusion

Our data show excellent clinical performance of the new fully automated bead-based immunoassay for the detection of antibodies in the diagnosis of PBC.

AUTO1-0092
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

VITAMIN D METABOLISM AND PAIN IN RHEUMATOID ARTHRITIS

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Background

Vitamin D deficiency has been implicated in the pathogenesis of autoimmune diseases, such as type 1 diabetes mellitus and scleroderma.Reduced vitamin D intake has been linked to increased susceptibility to development of RA, and vitamin D deficiency has been associated with higher disease activity.

Method

The objective of this study was to evaluate vitamin D status in patients with RA and assess the relationship between vitamin D levels and pain. In 45 patients with RA, 25(OH)D3 levels, parathyroid hormone levels, CRP and albumin were measured. Disease activity was evaluated by calculating the DAS28.

Results

45 patients were included in the study. 31 were in remission, 11 had painful joints and median VAS pain score of 30 (10–50). 41 patients had vitamin D levels <30ng/ml. Four had hyperparathyroidism. Levels of 25(OH)D3 were not found to be correlated with the DAS28 score (*p=0,59*), the VAS pain score (*p=0,55*) or CRP (*p=0,16*). PTH levels were positively correlated to CRP (*p=0,01*).

Conclusion

We found vitamin D deficiency to be highly prevalent in patients with RA but not linked to disease severity or pain. 36 months follow-up showed no association between vitamin D or PTH and death or osteoporotic fractures. PTH levels are related to CRP but not to the number of painful joints or VAS painscore. This relationship may reflect uncontrolled disease or be a reflection of physiological vitamin deficiency. Vitamin D supplementation may be needed both for prevention of osteoporosis and to better disease control in patients with RA and low levels 25(OH)D3 and high CRP.

AUTO1-0150
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

IMMUNOPATHOGENETIC FEATURES OF AUTOIMMUNE AND INFECTIOUS PHENOTYPES OF THE PATIENTS WITH A(HYPO)GAMMAGLOBULINEMIA.

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Background

The clinical manifestation of primary immunodeficiencies with a defect in antibody formation can be caused not only by severe long-term infectious lesions, but also by autoimmune diseases.

Method

Twenty-two patients were diagnosed with primary a- (hypo)gammaglobulinemia. The course of the disease of the 15 patients was manifested by frequent infections (infectious phenotype, IP). Two people were diagnosed with Crohn's disease, five patients
- rheumatoid arthritis (autoimmune phenotype, AP).

Results

A comparison of the parameters of immunity showed that in patients with AP, the number of T cells expressing the HLA DR more (AP -18 ± 2.1%, IP - 9 ±1.7%), and the number of T-reg is less than of patients with IP (AP 0.6 ± 0.3%, IP-1.1 ± 0.6%), which also demonstrates index Treg/CD4: AP-1.5 ± 0.4%, IP-3.7 ± 0.8%. In the conditions of the autoimmune manifestation, in comparison with infectious, expression of TLR2 (AP-80 ± 5%, IP-42 ± 3%), TLR4 (AP-60 ± 5%, IP-21 ± 7%), HLA DR (AP -80 ± 7%, IP-40 ± 4%) with monocytes, also the synthesis of IL-6 (AP-14 ± 2.6 pg / ml, IP-2.6 pg / ml), IFN-γ (AP -93 ± 5.9 pg / ml, IP - 78 ± 8.3 pg / ml) increases, while the serum content of IL-17 (16 ± 3.3 pg / ml) was determined only in patients with AP

Conclusion

The clinical manifestation of autoimmune processes of patients with a-(hypo)gammaglobulinemia is associated with weakening of T-immunosuppression, increasing of the activational indexes of T-lymphocytes and antigen-presenting cells, increasing of the production of proinflammatory mediators

AUTO1-0151
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ASSOCIATION OF ENDOTHELIN-1 AND CELL SURFACE ADHESION MOLECULES LEVELS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background

It is thought, that endothelin-1 (ET-1) has been implicated in the pathogenesis of inflammatory and fibrotic diseases, including systemic sclerosis (SSc). In addition to modulating vascular tone and extracellular matrix turnover, ET-1 up-regulates cell surface adhesion molecules - intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). The aim of this study was to investigate whether the serum ET-1 concentration is associated with the ICAM-1 and VCAM-1 levels in patients with systemic sclerosis.

Method

30 patients with systemic sclerosis (87% females and 13% male; age 52.5 ± 8.7 years) were included in the study. Serum samples were tested for autoantibodies to extractable nuclear antigens (ENA) by immunoblotting method (Euroimmun); serum levels of ICAM-1, VCAM-1 and ET-1 were assessed by enzyme immunoassay (BioSourse™ ; Biomedica).

Results

All systemic sclerosis patients were positive for ENA. Statistically significant correlation was estimated between soluble VCAM-1 and ET-1 concentrations (Spearman's correlation coefficient 0.687; $p<0.001$). There was no significant correlation between ICAM-1 and ET-1 levels ($p>0.05$).

Conclusion

The results of this study indicated that endothelin-1 and vascular cell adhesion molecule-1 are involved in the pathogenesis of systemic sclerosis and may be assessed together as markers of inflammation and identification of patients at the risk for disease progression.

AUTO1-0968
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

WHAT CAN A MULTIPLE ENDOCRINE SYNDROME HIDE?

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Background

Autoimmune poliglandular syndromes (APS) are endocrinopathies. Their original classification based on target endocrine organs has been changed according to genetic studies. Currently APS-1 is associated with an AIRE gene mutation, APS-2 is a polygenic dominant inheritance condition and APS-3 is subclassified according to organ-specific autoimmune diseases, namely endocrine, gastrointestinal (GI), skin and collagen. In turn, the majority of gastric neuroendocrine tumours are associated with autoimmune atrophic gastritis.

Method

Case report.

Results

A 35-year-old Portuguese female, with family history of Behçet disease and thalassemia minor, and a past history of repeated episodes of tonsillitis and chronic pyelonephritis, presented with widespread vitiligo since the age of 17. One year later she was diagnosed with Graves' disease treated sequentially with propylthiouracil, methimazole and radioactive iodine. At age 33 presented with asthenia, dyspepsia and nausea. Laboratory tests revealed microcytic hypochromic anaemia compatible with minor thalassemia. Thyroid function tests were normal. Upper GI endoscopy was positive for *Helicobacter pylori* and a gastric body sessile polyp was removed. The polyp was a well-differentiated neuroendocrine tumour (Ki67 low) with no evidence of metastasis (excluded by imaging and PET scan). One year later, repeat GI endoscopy revealed autoimmune gastritis and anti-parietal cells antibodies (Ab) were positive. A wide profile of auto-Ab to other endocrine organs were negative. Her final diagnosis is APS-3B+C: Graves' disease, autoimmune gastritis and vitiligo. Exome sequencing is awaited.

Conclusion

Current ongoing genetic classification of APS may provide important prognostic and therapeutic information. Their relationship to neuroendocrine tumours remains to be understood.

AUTO1-0554
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

EPIDEMIOLOGICAL AND CLINICAL FEATURES OF OVERLAP DISEASE. ABOUT 13 CASES

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Background

Overlap syndromes are an entity that satisfies the criteria of at least two connective tissue diseases. These conditions include systemic sclerosis , dermatomyositis or polymyositis, Sjogren's syndrome, rheumatoid arthritis and systemic lupus erythematosus.

Method

We examined 13 patients diagnosed with Overlap syndrome who consulted and/or were admitted in our department between 2011 and 2017.

Results

10 women and 3 men were included with mean age of 50 years (24-67 years old) and mean disease duration of 7 years. Diagnosis was made between 3 months and 1 year after symptoms appeared. Patients developed systemic sclerosis with polymyositis in 2 cases, scleroderma-systemic with lupus erythematosus and Sjogren's syndrome in 4 cases, scleroderma-systemic with lupus erythematosus in 4 cases and lupus erythematosus with rheumatoid arthritis in 3 cases. For the same patient different connective diseases were diagnosed simultaneously in 7 cases, but changed in 3 cases. The most common clinical manifestations included polyarthritis, myalgias, puffy fingers and Raynaud's phenomenon in 79%, 15%, 28.6% and 69% respectively. Pulmonary and renal manifestations were recorded in 53% and 15% respectively. ANA were positif in 9 cases and 7 patients had high anti-U1RNP antibodies levels. Treatments were different according to the clinics based on corticosteroids essentially. A case of death due to pneumonia was certified.

Conclusion

overlap syndrome is a rare entity. Over 6 years we recorded only 13 patients. Clinical aspects were different and so was the treatment, the challenge was the corticosteroids doses in the treatment of the scleroderma-systemic with lupus erythematosus and systemic sclerosis with polymyositis.

AUTO1-1046
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

A DASH OF AUTOIMMUNITY IN ALS

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Background

Amyotrophic lateral sclerosis (ALS) is a complex neurological disorder characterized by fatal degeneration of upper and lower motoneurons, with glia largely involved. Compromised astrocytic function as well as the interplay of immune-mediated mechanisms have been long recognised in ALS pathology. We demonstrated previously that IgG from sera of ALS patients enhance the mobility of acidic vesicles in cultured rodent astrocytes in a Ca^{2+} dependent manner.

Method

We investigated the acute effect of ALS IgG (0.1 mg/ml) on cytosolic calcium ($[Ca^{2+}]_i$) in brain cell cultures loaded with Fluo-4AM. Time-lapse images were obtained with 1 s time resolution 5 min before and up to 25 min after the application of ALS IgG.

Results

ALS IgG affected calcium homeostatic system in astrocytes through IP_3 mediated calcium release from the endoplasmic reticulum and entry of extracellular calcium through SOCE channels, with the activation of PLC-PI3K signaling cascade implicating receptor tyrosine kinase as the cell membrane trigger. In addition, all purified ALS IgG Fab fragments (0.01 mg/ml) evoked $[Ca^{2+}]_i$ changes, with some of them mimicking the effect of the whole IgG. Our ongoing studies also indicate alterations in $[Ca^{2+}]_i$ in primary microglial and hippocampal neuronal cell cultures by acute ALS IgG treatment. Transient calcium rise and/or an increase in spontaneous network activity of hippocampal neurons was induced.

Conclusion

Detailed characterization of calcium responses in different brain cell types will elucidate the mechanisms of subtle intercellular interactions and indicate promising diagnostic targets that might help in stratifying the patient cohort, and lead to personalized treatments.

AUTO1-0676
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

RECURRENT PERICARDITIS; STILL IDIOPATHIC ? THE PROS AND CONS OF A WELL-HONOURED TERM

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Background

Recurrent pericarditis is an inflammatory syndrome in which the spectrum of potential causes is wide and heterogenous. In developed countries more than 80% of cases of acute pericarditis remain without an established diagnosis after a conventional and standard diagnostic approach. These cases are generally labelled as 'idiopathic', e.g. without a known cause. This lack of information is a matter of concern for both patients and clinicians.

Method

Some years ago this term reflected the state-of-the art of scientific knowledge on the topic.

Results

Advances have changed this point of view, in light of available molecular techniques like PCR able to identify viral cardiotropic agents in pericardial fluid and biopsies, and recently because of the remarkable efficacy of IL-1 antagonists, a therapy targeting the innate immune response, which suggests clinical and pathogenic similarity between a proportion of patients with idiopathic recurrent pericarditis (IRP) and classical auto-inflammatory diseases.

Conclusion

it seems useful to discuss the pros and cons of using the term "idiopathic" in light of the new knowledge

AUTO1-0874
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

MIXED CONNECTIVE TISSUE DISEASE IN AN ADOLESCENT WITH LIP PALENESS

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Background

Background: Mixed connective tissue disease (MCTD) in the pediatric population is very rare and it is an important cause of morbidity. The disease is characterized by overlapping features of juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, systemic sclerosis, and juvenile dermatomyositis in the presence of high titres of anti-U1 ribonucleoprotein antibodies (RNP). Although Raynaud phenomenon (RP) most commonly affects fingers and toes, it can also affect the lips.

Method

We present a case of MCTD in a young girl whose first symptom was RP in lips.

Results

Case report: A 16-year-old girl presented with RP in fingers, toes, lips, which had started about six months earlier. The lips were especially pale. She manifested digital ulcers, hair loss, myalgia, and arthralgia. She had skin thickening on her face, and lip paleness. Her fingers were diffusely swollen with skin thickening, RP and digital pitting scars. She also had digital ulcers that improved spontaneously, alopecia, arthritis, and proximal muscle weakness. Her blood tests showed raised muscle enzymes. She had a multi-system work up including echocardiogram with pericardial effusion, obstructive pattern on lung function test, ground glass and linear opacities in lower lobes and esophageal ectasia in high-resolution computed tomography of the lungs. Motility studies showed reduced peristalsis in the esophagus. Nailfold capilaroscopy showed scleroderma pattern. The diagnosis of MCTD was made.

Conclusion

In our case, the complaint that led the patient to seek medical attention was the lip paleness. A high index of suspicion is important, since early diagnosis decreases morbidity and mortality in this disease.

AUTO1-0880
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

CREST SYNDROME IN A CHILD WITH PERSISTENT PAINFULL ULCER IN ELBOW

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Background

CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) is very rare in children, and the patients are considered to have limited cutaneous systemic sclerosis. Patients with limited scleroderma often develop calcinosis in soft tissues, usually complicated by skin ulceration.

Method

We report a case of an 11-year-old child with CREST syndrome. This child presented a non-healing ulcer that did not improve with the use of medications.

Results

An 11-year-old girl presented nodules on extensor surfaces of elbows, which had started about four years earlier. She also reported reddish coloration, sometimes bluish in fingertips induced by cold. Subsequently, the elbow nodules became a non-healing ulcer. On examination, she had an ulcer in right elbow with well-defined erythematous and edematous borders. She also presented telangiectasias in face and skin thickening on fingers. Serologic testing revealed a positive ANA in a centromere pattern (≥ 1/640). Motility studies showed gastric hypotonia with delay in emptying. Confirmation of calcinosis was made by elbow and knee radiographs showing lesions compatible with calcifications. The nailfold capillaroscopy showed SD pattern.

Conclusion

In our case report, the first symptom that caught the attention of the family was the appearance of calcinosis in elbows, with subsequent formation of an ulcer that did not heal with the use of medications. A high index of suspicion is relevant, since early diagnosis decreases morbidity and mortality in this disease. It is important that dermatologists, rheumatologists and pediatricians think about the possibility of CREST syndrome in patients with persistent non-healing ulcers of unknown cause.

AUTO1-0169
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ADHESION MOLECULE LEVELS AND ADIPOKINES IN SYSTEMIC LUPUS ERYTHEMATOSUS: RELATIONSHIPS WITH SEVERITY OF ILLNESS, AUTOIMMUNITY AND METABOLIC SYNDROME

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Background

The aim of this study is to assess whether the imbalance in adipokines and cell adhesion molecules (CAMs) determined by the presence of Metabolic Syndrome (MetS) could affect disease activity in Systemic Lupus Erythematosus (SLE) patients.

Method

One-hundred and twenty-six SLE patients were divided in two groups, with (n=64) and without MetS (n=62). Disease activity was determined using SLEDAI (SLE Disease Activity Index) considering the SLEDAI ≥10, which is indicative of severe disease. The CAMs PECAM-1, VCAM-1, ICAM-1, E-selectin and P-selectin and the adipokines MCP-1, hepatocyte growth factor (HGF), Lipocalin 2 (LCN2), adiponectin, leptin, resistin, TNF-α, IL-1, IL-6, IL-8, IL-10, PAI-1 and serum amyloid A protein (SAA) were evaluated.

Results

MetS patients had higher IL-8 (p=0.016), IL-10 (p=0.008), MCP-1 (p=0.002) and HGF (p=0.004). E-selectin (p=0.020) and P-selectin (p=0.049) were associated with the presence of MetS. MetS was not directly associated with disease activity measured by SLEDAI. ICAM-1 and LCN2 were lower and IL-6 and MCP-1 were higher in patients with SLEDAI ≥10. After binary logistic regression analyses, IL-6 (p=0.024), MCP-1 (p=0.027) and LCN2 (p=0.009) were associated with SLEDAI.

Conclusion

There is a different inflammatory profile between SLE and MetS that indirectly interferes in the inflammatory network and could favor the modification of disease activity.

AUTO1-0221
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

INFLUENCE OF HOMOCYSTEINE LEVELS ON ADHESION MOLECULES AND OXIDATIVE STRESS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Increased homocysteine levels, adhesion molecules and oxidative stress are considered important mechanisms contributing to the complex pathophysiological network that characterizes systemic lupus erythematosus (SLE). The aim of this study was to verify if homocysteine levels could influence the results obtained in the oxidative stress and in cell adhesion molecules in patients with SLE.

Method

The study included 176 subjects; 50 healthy individuals (control group) and 126 patients with SLE. Homocysteine levels, oxidative stress measurements, adhesion molecules and plasminogen activator inhibitor were determined. Hyperhomocysteinemia was categorizes using the median of SLE patients.

Results

Patients with increased homocysteine levels (≥10.59) presented higher hydroperoxides (p = 0.015), AOPP (p = 0.022), NOx (p = 0.011), PECAM-1 (p = 0.037), VCAM (p = 0.026), E-Selectin (p = 0.017), P-Selectin (p = 0.047), and lower TRAP values (p = 0.015) than patients with lower homocysteine levels (<10.59). In a binary logistic regression that included the markers and parameters with statistical relevance between the groups with homocysteine <10.59, as a reference group, and homocysteine ≥ 10.59, TRAP (OR= 95% CI: 0.976; p =0.006) was found as inversely associated, whereas hydroperoxides (OR= 95% CI: 1.000; p=0.012), NOx (OR= 95% CI: 1.122; p =0.027), and PECAM-1 (OR= 95% CI: 1.000; p=0.004) were found to be directly associated.

Conclusion

The behavior of some adhesion molecules and oxidative stress markers depends in a large scale of homocysteine levels. The data obtained in the present study allow suggesting that special efforts may be directed to decrease homocysteine levels in SLE.

AUTO1-0528
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

INCREASED ADHESION MOLECULE LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS: RELATIONSHIPS WITH SEVERITY OF ILLNESS, AUTOIMMUNITY AND CORTISOL LEVELS

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Background

The aim of this study is to delineate disorders in adhesion molecules in systemic lupus erythematosus (SLE) and to assess whether cortisol, nuclear autoantibody (ANA) titers and the metabolic syndrome (MetS) are associated with adhesion molecules in SLE

Method

48 healthy individuals and 171 SLE patients were enrolled. Disease activity was determined by SLEDAI (SLE Disease Activity Index) score. CAM and cortisol levels were evaluated.

Results

Platelet endothelial cell adhesion molecule 1 (PECAM-1), Vascular cell adhesion molecule 1 (VCAM-1), E-selectin, P-selectin and Plasminogen activator inhibitor type-1 (PAI-1) were significantly higher in SLE patients. These significant differences could not be explained by the drug treatment. Mycophenolate treatment significantly decreased intercellular adhesion molecule 1 (ICAM-1) and increased E-selectin levels. Binary logistic regression analysis showed that PECAM-1 and PAI-1 predicted SLE with a sensitivity of 86.5% and a specificity of 81.3%. ANA was significantly and positively associated with PECAM-1, VCAM-1, E-selectin, and PAI-1, whilst cortisol was negatively associated with PCAM-1 and ICAM-1. There were significant associations between MetS and E-selectin and PAI-1. 18.2% of the variance in SLEDAI score was explained by increased PECAM-1 values and DNA titers and the MetS

Conclusion

Our data confirm that CAM play a role in the pathophysiology of SLE and show that they are increased, especially PECAM-1. MetS, ANA, and cortisol modulate the CAM concentrations but do not explain the increased levels in SLE Increased levels of CAM are a new drug target in SLE.

AUTO1-0803
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

RELATION BETWEEN ANTINUCLEAR ANTIBODIES AND SIGNS AND SYMPTOMS IN PATIENTS WITH SYSTEMIC SCLEROSIS (SSc)

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Background

Determine the ANA patterns present in a group of patients with systemic sclerosis and their relation with signs and symptoms. SSc is a connective tissue disease, which involves the skin, joints and internal organs such as the gastrointestinal tract, lung, the heart and the kidney, the increase of collagen translated into thickening of the skin, alteration of small arteries and microcirculation with anatomopathological characteristics.

Method

122 samples were tested from patients with systemic sclerosis and 50 samples from healthy donors. Three different techniques were done for the evaluation: ELISA, Immunofluorescence and Immunoblot from AESKU Diagnostics with the SQ2 and Helios Systems.

Results

118 samples obtained a positive result in the ANA test. They were classified as systemic sclerosis related to the presence of autoantibodies. In the group of healthy donors, all the results for ANA were negative.

Centromere pattern and anti-topoisomerase 1 pattern were the most frequent patterns reported and its symptoms were associated with limited and diffuse SSc respectively. All samples were confirmed and correlated with ELISA results.

Conclusion

The presence of autoantibodies is highly specific in order to help in the diagnosis and classification of patients with systemic sclerosis compared with a normal population.

The correlation of the patterns determined by IFA with techniques such as Elisa and blot was very good, finding a concordance close to 100%, which confirms that immunofluorescence is an adequate test for the screening of autoimmune diseases.

AUTO1-0186
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ACTIVE MULTIPLE SCLEROSIS IS ASSOCIATED WITH CHRONIC RHINOSINUSITIS PLUS JEJUNODUODENAL REFLUX

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Background

Multiple Sclerosis (MS) has been associated with Chronic Rhinosinusitis (CRS)[1] which is itself associated with gastro-oesophageal reflux.[2] We investigated whether patients with MS present more frequently with CRS and jejunoduodenogastric reflux (JDGR).

Method

All patients consulting a private gastroenterologist and presenting with MS were prospectively enrolled into a prospective 5 years cohort study.

Periodontitis, Helicobacter pylori (HP) infection (Prontodry ®; MIC France) and presence of Propionibacterium acnes (PA) on the tongue (fluorescence with a Wood lamp) were noted. A medical history of oral herpetic lesions (HSV) or of early (before 12 years of age) severe dental cavities (ESDC) was collected.

The control group includes 2118 patients who underwent similar investigations and data collection during the same period.

Results 22 patients with MS were enrolled; ten with an active disease. Age (51 +/- 13 versus 50 +/- 16), weight (51 +/- 13 versus 63 +/- 15) and gender (70% versus 69.8%) were similar in both groups. Patients with MS present more frequently with CRS (68.2 versus 27.5%), CRS+JDGR (50.0 versus 28.4%) and PA (54.5 versus 10.9). See table.

Patients with active MS have more ongoing CRS+JGDR (80.0 versus 25%; p<0.02).

Table: Description of the results according to the diagnosis of HSV, CRS, JDGR, PA, ESDC, HP or periodontitis (in %)

Diseases (number of patients)	HSV	CRS	JDGR	PA	ESDC	HP	Periodontitis	CRS+JDGR
MS (22)	59.1*	68.2§	59.1*	54.5!	59.1*	36.4*	31.8*	50.0§
Control group (2118)	39.2	27.5	41.6	10.9	38.0	21.0	20.7	28.4

***P<0.05; § p<0.01; ! p<0.001**

Conclusion

MS (especially when active) is associated with CRS+JDGR.

The impact of the control of CRS+JDGR on the evolution of MS should be further investigated.

1. Gay D et al. Lancet. 1986 Apr 12;1(8485):815-9
2. Leason SR et al. Rhinology. 2017 Mar 1;55(1):3-16

AUTO1-0916
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

T-HELPERS AND REGULATORY T-CELLS INFLUENCE ON B-LYMPHOCYTES SUBSET PATTERN OF PERIPHERAL BLOOD AND THYROID IN GRAVES DISEASE

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Background

Graves disease (GD) is an auto-antibody-mediated disease where autoantibodies are produced against the thyroid stimulating hormone receptor (TSHR). B cells play an essential role in GD by virtue of their pathognomonic activating autoantibodies against the TSHR. Aim: to compare the helper- (Th-cells) and regulatory T-cells (Treg) effects on the B lymphocytes phenotypic composition of p*eripheral* blood and thyroid tissue in patients with GD.

Method

Fourty three women with GD and 67 healthy women as a control were examined. Th-cells, Treg and B-lymphocytes phenotypic composition were measured using direct immunofluorescence of whole peripheral blood and lymphocytes isolated from thyroid tissue, using direct immunofluorescence.

Results

In patients with GD the relative amount of Treg in the thyroid tissue corresponds to their level in p*eripheral* blood. The percentage of B1-cells in thyroid tissue was reduced compared to their level found in p*eripheral* blood, but with an increased level of memory B-cells ($p<0,05$). According to the CD23 marker, in p*eripheral* blood of patients with GD reduces the number of activated B-lymphocytes. It was found that the relative number of activated B cells in the thyroid tissue was low in compare to their blood level in patients with GD ($p<0,001$).

Conclusion

This view provide the reasons for discarding the traditional simplistic dichotomous view of the T helper type 1 and 2 pathways (Th1/Th2) and will focus on the role of the recently characterized peripheral blood and thyroid T cells, Treg and activated B lymphocytes, and, also, organ-specific autoimmunity in GD.

AUTO1-0776
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

MALONDIALDEHYDE-CONJUGATED WITH ALBUMIN INDUCE A PRO-INFLAMMATORY ACTIVATION OF T CELLS FROM HUMAN ATHEROSCLEROTIC PLAQUES THROUGH BOTH A DIRECT AND A DENDRITIC CELL-MEDIATED MECHANISM.

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Background

Activated dendritic cells (DCs) and T-cells occur in atherosclerotic plaques and could play an important role in plaque erosions, rupture and cardiovascular disease (CVD). Oxidized low density lipoprotein (OxLDL) activates T-cells from human plaques but it is unclear which role different components in OxLDL play, though malondialdehyde (MDA) which forms adducts with proteins is implicated. We therefore study MDA conjugated with a common human protein, albumin (MDAHSA). Heat shock protein 60 (HSP60) may play a role in atherosclerosis-related immunity.

Method

Human DCs were differentiated from blood monocytes and treated with MDAHSA. Autologous T-cells from human plaques or blood were co-cultured with the pre-treated DCs or treated directly.

Results

MDAHSA induced a pro-inflammatory DC-mediated T-cell activation as determined by FACScan and cytokine production. There was also a strong direct effect on Tcells. Toll like receptors 2 and 4 were induced in both T-cells and DC by MDAHSA. Both an inhibitor of oxidative stress and antibodies against MDA inhibited MDAHSA-induced direct T-cell activation. HSP60 was strongly induced in T-cells activated by MDAHSA directly, while effects on DC were weak. After initial activation, MDAHSA induced apoptosis in both DCs and T-cells. Atherogenic M1 macrophages were induced by MDAHSA.

Conclusion

MDAHSA promotes immune activation, of DCs and T-cells in plaques (the latter especially by a direct mechanism), and also induction of atherogenic M1 macrophages. Antibodies to MDA inhibited MDAHSA effects on T-cells. Inhibition of MDA-effects by immunization or other types of inhibition could be a therapeutic option.

AUTO1-0992
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ALOPECIA AREATA AND AUTOIMMUNE COMORBIDITIES: A CLINICAL STUDY IN A TRICHOLOGY UNIT

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Background

Alopecia Areata (AA) is the most common cause of autoimmune localized, nonscarring alopecia. Several autoimmune diseases (AD) have been associated to AA. To characterize in a real-life-setting the development of AD in a cohort of patients with AA total or universalis.

Method

We retrospectively reviewed the records of AA patients managed in the Trichology Unit of the Ramon y Cajal Hospital (Madrid), between January 1998 and December 2017. Clinical and biological data were retrospectively collected with a standardized form, by the same clinicians. Concomitant AA and AD was established as less than 1 year among the 2 diagnoses.

Results

The study included 61 patients with AA, which AA universalis was the most frequent (54/61). Female were predominant (40 cases, 66%). The mean age was 37±12 years. 26 AD was documented in 20 patients, including autoimmune hypothyroidism (N = 12), atopic dermatitis (N = 5), vitiligo (N = 3), type 1 diabetes mellitus (N=2), asma (N = 1), chronic urticaria (N = 1), psoriasis (N = 1) and eosinophylic esophagitis (N=1). AD was more frequent in women (45% vs 9%, p = 0.005) and in younger patients (34 vs 38 years, p = 0.1).

Conclusion

In the analyzed patients with AA of our center, almost 1 out of 3 patients with AA developed AD. The spectrum of autoimmunity associated with AA was quite broad, being the autoimmune hypothyroidism the most prevalent. Younger age and female were more associated with AD in our cohort.

AUTO1-0219
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

BULLOUS PEMPHIGOID AND DEMENTIA: RELATIONSHIP BETWEEN SKIN AND BRAIN PEPTIDES

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Background

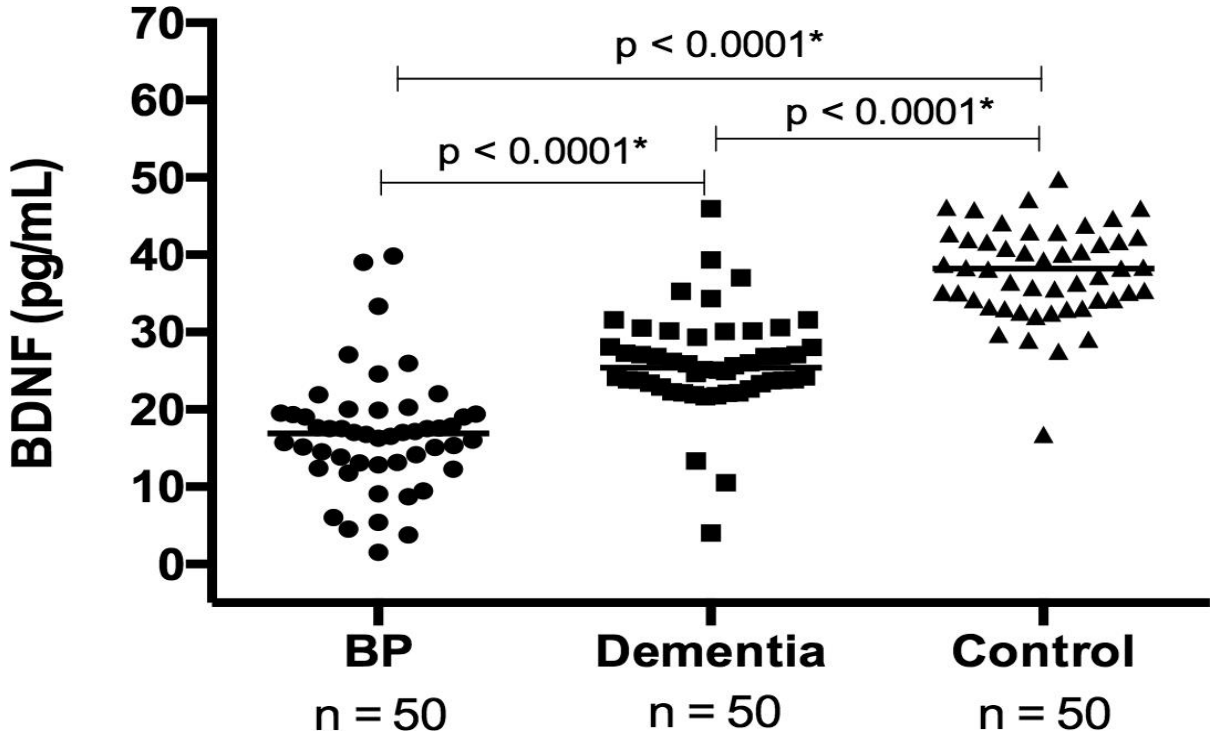
Bullous pemphigoid (BP) results from the production of autoantibodies against BP180/230 hemidesmossomal proteins, affects the elderly and is associated with neurological diseases (ND), mainly dementia. Decreased concentration of BDNF (brain-derived neurotrophic factor) - neurotrophin responsible for genesis and neuronal survival, has been related with ND. The aim of this study was to verify BDNF peptide and anti-BP180/230 autoantibodies in the relationship between BP and dementia diseases.

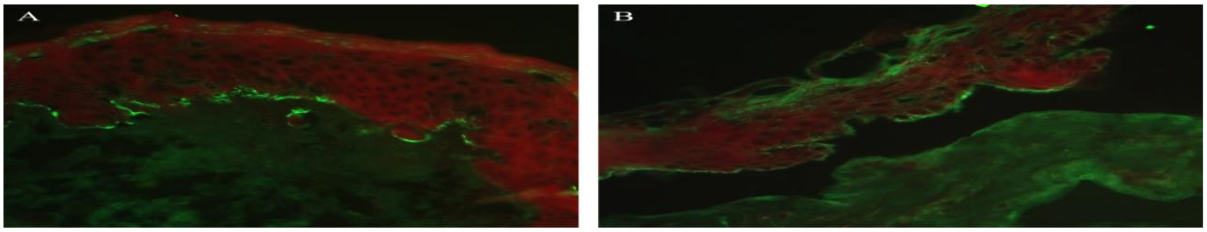
Method

A comparative study enrolled 50 patients with BP, 50 with dementia and 50 elderly controls. ELISA quantified BDNF (R&D System-Germany) and IgG anti-BP180/230 (MBL-Japan) in serum samples.

Results

BP group assembled 26% of ND (dementia 16%, stroke 6% and epilepsy 4%) preceding BP diagnosis. BDNF values were lower in BP (16.88pg/mL) compared to dementia group (25.41pg/mL) (p=0.0001); both were lower than controls (38.21pg/mL) (p=0.0001each) (Figure 1). Anti-BP180/230 positivity was observed in BP (74%, 40%, respectively), and in dementia (10%, 10%) group and controls (14%, 0%). Moreover, in two of 10 dementia patients with anti-BP 180/230 positivity, indirect immunofluorescence-Salt-Split-Skin (IIF-SSS) showed IgG fluorescence in the epidermal side of cleavage configuring BP pattern (Figure 2). IIF-SSS was negative in controls.





Conclusion

Considering that the BP group presented the lowest BDNF values, some immunological event may be involved in triggering BP disease following dementia. Our results suggest that dementia patients presenting serum positivity for anti-BP180/230 antibodies or BP pattern on IIF-SSS could be a population at risk for BP disease. Therefore, a molecular mimicry between BP180/230 peptides in the skin and nervous system may be allied with BP pathogenesis.

AUTO1-1008
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ANTI-GM1 IgG ANTIBODIES IN NEUROLOGIC DISEASES

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Background

Though GM1 is a major ganglioside in the central nervous system (CNS) of higher vertebrates, CNS disease associated with anti-GM1 antibodies are rarely reported. Nevertheless, there are several reports describing acute disseminated encephalomyelitis with high titer anti-GM1 IgG antibodies. To investigate whether anti-GM1 IgG antibodies are related to a specific entity, we inspected its presence in various neurologic diseases.

Method

Between January 2010 and December 2016, a total of 1604 patients underwent serum anti-GM1 IgG ELISA tests at Seoul National University Hospital, South Korea. An absorbance ratio of > 50% was used as the cut-off value. Using the International Classification of Diseases-10 code, diseases were classified into acute demyelinating encephalomyelitis (ADEM), encephalitis of infectious and non-infectious diseases, CNS neoplasm, cerebellar ataxia, cranial neuropathy, meningitis, stroke, myelopathy, acute inflammatory demyelinating polyneuropathy (AIDP), chronic inflammatory demyelinating polyneuropathy (CIDP), motor neuron disease, multifocal motor neuropathy, neuromuscular junction disease, other peripheral neuropathy, myopathy, and other transient (vertigo, loss of consciousness, headache, etc.) or long-lasting (e.g. cognitive decline) neurologic disease of undetermined causes.

Results

Stroke, ADEM, and AIDP showed a high percentage of anti-GM1 IgG antibody-positive cases (23.5%, 21.4%, and 17.7%, respectively), while none of the cases of meningitis, myopathy, and neuromuscular junction disease showed positive results. The other categories showed positive results in 3.4% to 11.8% of the cases.

Conclusion

Positive anti-GM1 IgG antibody results were mostly observed in acute neurologic diseases, whether demyelinating (ADEM or AIDP) or non-demyelinating (stroke). Evaluating the presence of the antibody may guide clinicians in diagnosing neurologic diseases.

AUTO1-0450
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ANA-SPECIFIC ANTIGEN RECOGNITION IN PATIENTS WITH PSORIASIS AND PSORIATIC ARTHRITIS USING A MULTIPLEX LINE IMMUNOASSAY SPECIFICALLY DESIGNED FOR ANA ASSESSMENT AS PER ICAP

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Background

The nuclear antigen-specificities of ANA in patients with psoriasis (Ps) and psoriatic arthritis (PsA) are not defined. ICAP has reported a consensus of 14 anti-nuclear antibody immunofluorescence (IF) patterns and commercial molecular-based multiplex assays were developed to assist ICAP's IF ANA testing.
Aim: To test ANA in Ps and PsA patients using a recently developed multiplex immunoassay specifically designed for ANA testing as per ICAP.

Method

A total of 70 patients (38 female) with Ps (n=36) or PsA (n=34) and 50 demographically matched normal controls (NCs) were tested by an ANA line immunoassay containing 23 different antigens: dsDNA, nucleosomes, histones, SS-A, Ro-52, SS-B, nRNP/Sm, Sm, Mi-2α, Mi-2β, Ku, CENP A, CENP B, Sp100, PML, Scl-70, PM-Scl100, PM-Scl75, RP11, RP155, gp210, PCNA and DFS70.

Results

Overall, reactivity to at least 1 against antigen was found in 23/70 patients (32.9%) compared to 6/50 (12%) NCs (p=NS; Ps vs PsA, p=NS). Specifically, the ICAP-related abs in Ps/PsA patients were as follows: AC-1:4.3%; AC-2:10%; AC-3:0.7%; AC-4:11.4%; AC-5:0.7%; AC-6:0.7%; AC-8:2.8%, and AC-10: 2.1%, while in NCs ICAP-related abs were as follows: AC-2:4%; AC-4:4%, AC-3:2%; AC-8:2% and AC-11:2% pattern. There was no statistically difference for the presence of ICAP between Ps and PsA and between Ps/PsA and NCs.

Conclusion

ICAP's ANA nomenclature is a helpful tool for ANA reporting in patients with Ps and PsA but does not reveal a dominant target of ANA in these diseases.

AUTO1-0381
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

GLYCAN STRUCTURE OF MYELIN OLIGODENDROCYTE GLYCOPROTEIN (MOG) AND ITS IMPACT ON AUTOANTIBODY RECOGNITION

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Background

Autoantibodies against myelin oligodendrocyte glycoprotein (MOG) are found in a proportion of patients with different neuroinflammatory diseases. Here, we identified the glycan structure of MOG and analyzed the effect of different mutations on the glycosylation site N31 on autoantibody recognition.

Method

Myelin from human brain was obtained by density gradient and myelin glycoproteins were obtained by lectin-chromatography. The extracellular part of MOG was produced in HEK cells. Using MALDI-TOF/TOF-MS and LC-MS/MS we identified the glycan structures present in MOG derived from HEK cells and human myelin. Autoantibodies against MOG were identified using MOG-transfected HeLa cells. Reactivity to wild-type MOG and different mutants of the glycosylation site (N31D, N31A) were quantified by flow cytometry.

Results

Different glycan structures were identified in recombinant MOG, mostly core fucosylation with sialic acids on the antenna. In myelin MOG, the core fucose was also present and all the glycans had a bisecting GlcNAc. Response to glycosylation-deficient MOG was analyzed in 16 patients with autoantibodies to MOG. Six of them showed a higher reactivity against both unglycosylated mutants, N31D and N31A. One patient reacted lower to N31D than to wild-type MOG, but higher to N31A.

Conclusion

Mass spectrometry revealed differences between the glycan structures in recombinant and myelin MOG. Glycans of MOG might regulate its binding to interaction partners. The sugar attached to MOG was not recognized by any of the patients; however, it constituted a sterical hindrance to MOG-recognition in some patients. The comparative analysis of N31A and N31D showed a further heterogeneity of anti-MOG reactivity.

AUTO1-0659
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

IMMUNOLOGICAL CHARACTERIZATION OF IgA NEPHROPATHY PATIENTS

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Background

IgA Nephropathy (IgAN) is the leading form of primary glomerulonephritis affecting glomerular mesangium, with proteinuria, hematuria, hypertension and reduction of renal glomerular filtrate. Approximately 40% of cases are related to end-stage renal failure, requiring either dialysis or renal transplantation.The gold-standard technique for IgAN diagnosis is renal biopsy. In the last years, the better knowledge of the disease, has led several authors to describe serum biomarkers that may be useful for diagnosis and prognosis, such as levels of partially degalactosilated IgA1 (Gd-IgA1). Until now, it has not been performed an exhaustive analysis of peripheral leukocyte subpopulations and CD89 expression on monocytes.

Method

A prospective study of 22 patients diagnosed of IgAN by renal biopsy has been performed. By flow cytometry of whole blood, immunophenotype of leukocyte subpopulations and CD89 expression in three monocytes subpopulations has been characterized. Analysis of serum levels of Gd-IgA1 has been performed with commercial kit of ELISA, *Gd-IgA1 Assay kit-IBL.*

Results

The results of this study have shown that those patients with poor renal function and more severe renal biopsy have lower Mean Fluorescence Intensity (MFI) of CD89 on non-classical monocytes. The immunophenotype showed that patients had a higher percentage of activated and effector memory $CD4^+$ and $CD8^+$ lymphocytes, lower percentages of B transitional lymphocytes and plasmablasts, and higher percentages of NK lymphocytes $CD56^{dim}CD16^+$ and myeloid dendritic cells.

Conclusion

In conclusion, this preliminary study shows that MFI of CD89 on non-classical monocytes could be used as a prognostic biomarker of IgAN. In parallel, the immunophenotype maybe useful for IgAN diagnosis.

AUTO1-1057
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

EXPRESSION AND ACTIVATION OF THE AIM2 INFLAMMASOME IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is an inflammatory disease in which the IL-1B contribute with inflammatory process and bone erosion. Release of active mature IL-1B is dependent on AIM2-inflammasome activation. And AIM2 activity alterations are associated to autoimmune disorders such as Systemic Lupus Erythematous, however its role in RA has not been describe. The aim of this study was evaluated AIM2 expression and activity in RA patients and control subjects.

Method

Inflammasome expression AIM2 was evaluated in monocytes (CD14 +) by flow cytometry, the activity was determined by measuring IL-1β levels in the supernatant of monocyte cultures stimulated with an agonist specific for the inflammasome, using a quantitative ELISA. In addition, caspase activity was assessed by western blot in cells from healthy subjects and patients with RA.

Results

Flow cytometry analysis shows a statistically significant decrease in the expression of CD14 + AIM2 + cells in RA patients compared to control subjects. In addition, a decrease in CD14 + AIM2 + cells was observed in patients with active disease (DAS28> 4.0) and with late disease (<2 years) with respect to control subjects. With respect to AIM2 activity, increased levels of IL-1 were detected in monocyte cultures of RA patients compared to control subjects. No correlation was observed between the percentages of CD14 + AIM2 + cells and the clinical parameters of patients with RA

Conclusion

Our results suggest that patients with RA show a negative regulation in the expression of AIM2 associated to the activity and to the evolution of the disease.

AUTO1-0057
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

Evaluation of HLA-G in Systemic Sclerosis

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Background

Systemic sclerosis (SSc) is characterized vascular damage, immune dysregulation and fibroblasts activation. HLA-G is expressed on extravillous cytotrofoblast, in placenta but also in a few normal tissues, solid tumours, transplanted organs and virally infected cells. Soluble form (sHLA-G) derives from shedding of cleaved surface isoforms (sHLA-G1) or secretion of soluble isoforms (HLA-G5). Immunosuppressive functions have been attributed to both membrane HLA-G (mHLA-G) and sHLA-G.

Method

Thirtyfive patients (28 females/7 males, age 40-89 years) with diffuse SSc (dSSc, n. 12) or limited SSc (lSSc, n. 23) and 40 healthy sex and age matched controls were enrolled. Plasma sHLA-G, sHLA-G1 and HLA-G5 levels were determined by immunoenzymatic assays. mHLA-G expression in peripheral blood mononuclear cells (PBMC) was evaluated by flow cytometry.

Results

sHLA-G were significantly higher in SSc patients than in controls (444.27 ± 304.84 U/ml, 16.74 ± 20.58 U/ml, respectively, $p < 0.0001$). In SSc patients, sHLA-G1 and HLA-G5 were comparable (264.66 ± 226.95 U/ml, 181.44 ± 130.12 U/ml, respectively). sHLA-G levels did not correlate with disease duration and no significant differences were detected between dSSc or lSSc patients. Percentage of HLA-G-+ monocytes (0.98 ± 1.72), CD4+ (0.37 ± 0.68), CD8+ (2.05 ± 3.74) and CD4+CD8+ cells (14.53 ± 16.88) was significantly higher in SSc patients than in controls (0.11 ± 0.08, 0.01 ± 0.01, 0.01 ± 0.01 and 0.39 ± 0.40, respectively) ($p < 0.0001$).

Conclusion

These data indicate that in SSc secretion and/or shedding of sHLA-G and mHLA-G are clearly elevated and involved in immune dysregulation.

AUTO1-0965
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

SELECTIVE IGM DEFICIENCY: THE TIP OF THE ICEBERG.

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Background

Primary Immunodeficiencies (PID) in adults should be suspected when repeated infections and autoimmunity come together. Immunoglobulin M (IgM) provides the initial response to foreign antigens and plays a regulatory role, preventing autoimmune responses.

Method

Case report

Results

In 2016, a 44 year-old male was referred to our unit due to recurrent infections and cytopenias. Apart from obesity he was healthy. At age 38 he developed an EBV infection associated to pancytopenia; at age 40 he required hospital admission due to urinary sepsis, when a 4000/µL platelet count and anti-platelet antibodies were found. The bone marrow aspirate was normal and he responded to steroids. In the span of 2 years that followed he suffered acute bacterial epidendimytis, two urinary tract infections and another episode of severe thrombocytopenia (5000/µL platelet count). Our investigation revealed a normal full blood count. There was no circulating IgM, a finding repeatedly confirmed over the course of one year, all other immunoglobulins being within the normal range. Secretory IgA was present and flow cytometry displayed normal subsets with IgM-expressing B-cells. No other auto-antibodies were found. A Kariotype anomaly (XY,inv[9],p11q13) was not associated to any other mutation (by exome sequence of PID genes). Several rare variants were found in heterozygosity: NFATC1, TMC8 and TBX21, predictably not pathogenic. There was no evidence for EBV reactivation. As a general prophylactic measure for infections and thrombocytopenic episodes, IVIG has been recommended.

Conclusion

The etiology of selective IgM deficiency is obscure with a likely genetic cause. It remains a very rare cause of PID.

AUTO1-0193
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

CONTRIBUTION OF DIAGNOSTIC TESTS FOR THE ETIOLOGICAL ASSESSMENT OF UVEITIS, DATA FROM THE ULISSE STUDY

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Background

Our aim was to evaluate the diagnostic yield of the tests prescribed for the etiologic diagnosis of uveitis in the ULISSE study.

Method

ULISSE is a prospective study that assessed the efficiency of a two steps' standardized strategy compared to an open strategy for the etiologic diagnosis of uveitis. We reported the relevance of the diagnostic tests used in the standardized strategy, as well as the profitability of the tests that were prescribed to more than twenty patients in each group.

Results

Among the first step's systematic tests, tuberculin skin test was the most contributive investigation (17.1%), followed by chest X-ray (8.4%), C reactive protein and erythrocyte

sediment rate (6.6% and 5.1%), complete blood count (2.2%) and VDRL (2.0%). The second step's most often contributive tests were: HLA B27 (56.3%), chest-CT (30.3%) and angiotensin converting enzyme (16.5%). Immunological tests were never contributive. Among the investigations guided by clinical or paraclinical findings, the most often contributive tests were: Quantiferon® (24%), electrophoresis of serum protein (7.8%) and sacroiliac imagery (46.4%). Intracellular serologies (1.7%), serum calcium (2.1%) and hepatic tests (3.3%) were exceptionally contributive. Among the third intention tests, labial salivary gland biopsies were contributive in 17.9% of cases, but the profitability of other invasive investigations or specialized imagery could not be determined since these tests were rarely performed.

Conclusion

Only a few diagnostic tests are usefull for the etiological assessment of uveitis. Some tests are never or exceptionally contributive. Further studies are required to evaluate the profitability of specialized imagery and invasive investigations.

AUTO1-0806
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

THE DIAGNOSTIC VALUE OF THE AESKULISA PR3 SENSITIVE AND AMP; AESKULISA MPO IN THE EUVAS-COHORT

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Background

Anti-neutrophil-cytoplasmic-antibodies directed against proteinase-3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) are serological hallmarks of small vessel vasculitis, particularly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). In a recent multicentre European-Vasculitis-Study-Group (EUVAS) evaluation, the performance of IIF was compared to that of various antigen-specific immunoassays. The aim was to evaluate the diagnostic accuracy of the third-generation antigen-specific immunoassays PR3-ANCA (AESKULISA-PR3-sensitive) and MPO-ANCA (AESKULISA-MPO) and to compare these data with the results from the other assay (Orgentec).

Method

257 samples from the EUVAS cohort were tested for the presence of ANCA by PR3-ANCA ELISA (AESKULISA-PR3-sensitive) and MPO-ANCA ELISA (AESKULISA-MPO). Newly diagnosed GPA/MPA (n=66) patients and diseased controls (n=191): systemic lupus erythematosus (n=60), systemic sclerosis (n=10), rheumatoid arthritis (n=90), Scleroderma (n=11) and Sjögren's syndrome (n=30) were analyzed.

Results

In AAV patients, ANCAs were detected with both methods in 56 cases; divergent results were obtained in only 1 patient sample. 191 patients with other rheumatic diseases were analyzed and only 13 vs 11 (AESKU/Orgentec) were positive for ANCA (SLE, sclerosis, RA, RA/RV). This study shows that the PR3- and MPO-ANCA ELISA are highly specific (93.2%/94.2%) and sensitive (85.9%/85.9%) in the detection of ANCA to identify AAV or conditions known to be associated ANCA.

Conclusion

Our comparison of PR3- and MPO-ANCA ELISAs showed (i) a high diagnostic performance of these PR3- and MPO-ANCA ELISAs to discriminate AAV from disease controls. (ii) very good correlation between the other methods tested. In conclusion, these novel assays can be used as screening method for detection of ANCA-associated diseases.

AUTO1-0844
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

PHYSICAL ACTIVITY AND AUTOIMMUNE DISEASES: GET MOVING AND MANAGE THE DISEASE

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Physical activity, by definition, is any skeletal muscle body movement that results in energy expenditure. Recent research highlights the salient role of modifiable behaviors such as physical inactivity on various aspects of the immune system and autoimmune diseases. Physical activity leads to a significant elevation in T-regulatory cells, decreased immunoglobulin secretion and produces a shift in the Th1/Th2 balance to a decreased Th1 cell production. Physical activity has been shown to be safe in all ADs. The incidence of Rheumatoid arthritis (RA), multiple sclerosis (MS), inflammatory bowel diseases (IBD) and psoriasis has been found to be higher in patients less engaged in physical activity. Physically active RA patients were found to have a milder disease course, better cardiovascular disease (CVD) profile, and improved joint mobility. Physical activity decreases fatigue, enhances mood, cognitive abilities and mobility in patients with MS. In SLE patients, enhanced quality of life and better CVD profile were documented in more physically active patients. Physically active patients with type 1 diabetes mellitus have a decreased risk of autonomic neuropathy and CVD. Both fibromyalgia and systemic sclerosis patients report decreased disease severity, pain, as well as better quality of life with more physical activity. Further, SSc patients improve their grip strength, finger stretching and mouth opening with increased level of exercise. The purpose of this paper is to review the clinical evidence regarding the safety, barriers to engagement, and impact of physical activity on autoimmune diseases.

AUTO1-0435
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

METABOLIC SYNDROME AND THE DECREASED LEVELS OF URIC ACID BY LEFLUNOMIDE FAVOR REDOX IMBALANCE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is a disabling autoimmune inflammatory disease characterized by a chronic involvement of the synovial joints that may lead to joint destruction and functional decline. RA patients show redox imbalance, indicating a pathogenic role of oxidative and nitrosative stress in RA. Although there are few studies reporting the effects of drug treatment on oxidative stress in patients with RA, most are able to demonstrate that the reduction in disease activity after drug therapy is associated with reduced indices of oxidative stress and inflammation. Furthermore, studies have demonstrated that the pro-inflammatory milieu and oxidative stress favor detrimental changes in metabolism, such as metabolic syndrome (MetS).The aim of the present study was to verify the influence of MetS and drugs on nitrosative and oxidative biomarkers in patients with RA.

Method

177 patients with RA and 150 healthy volunteers participated in this study, which measured lipidic hydroperoxides, advanced oxidation protein products (AOPP), nitric oxide metabolites (NOx), carbonyl protein, total radical-trapping antioxidant parameter (TRAP), uric acid (UA).

Results

NOx and the NOx/TRAP ratio were significantly increased in RA, whilst no significant differences in AOPP, UA and TRAP levels were found between both groups. Leflunomide use was associated with increased levels of carbonyl protein, and lowered levels in TRAP and UA, whilst the NOx/TRAP ratio further increased. MetS was accompanied by increased AOPP and UA levels.

Conclusion

NOx and NOx/TRAP are strongly associated with RA physiopathology. In addition, the presence of MetS and decrease in levels of UA by leflunomide favor redox imbalance in RA patients.

AUTO1-0447
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

CELL ADHESION MOLECULES AND PLASMINOGEN ACTIVATOR INHIBITOR TYPE-1 (PAI-1) IN PATIENTS WITH RHEUMATOID ARTHRITIS: INFLUENCE OF METABOLIC SYNDROME

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory and systemic disease characterized by endothelial activation. The main objective of this study was to verify the profile of cell adhesion molecules (CAM) in RA patients, and the influence of metabolic syndrome (MetS) and drugs used in the treatment of RA in this profile. A second objective was to propose models of prediction of activity in RA using these biomarkers.

Method

115 healthy individuals and 144 RA patients were enrolled. Disease activity was determined by DAS28 (disease activity score 28) based on erythrocyte sedimentation rate (DAS28-ESR) or C- reactive protein (DAS28-CRP). Serum CAM and plasminogen activator inhibitor type-1 (PAI-1), anthropometric and immunological parameters were measured.

Results

Vascular cell adhesion molecule 1 (VCAM-1) was significantly decreased and PAI-1 was significantly higher in RA patients as compared to controls. Binary logistic regression analysis showed that VCAM-1, CRP, and tumor necrosis factor-α (TNF-α) predicted RA with a sensitivity of 95,9% and a specificity of 89,5%. 42,9% of the variance in DAS28-ESR and 49,2% of the variance in DAS28-CRP is explained by increased PAI-1, TNF-α, body mass index and decreased platelet endothelial cell adhesion molecule 1 (PECAM-1). MetS is characterized by increased PAI-1, E-selectin and P-selectin levels.

Conclusion

Our data show that lower levels of VCAM-1 are associated with RA independently of MetS, while increased PAI-1 and lowered PECAM-1 are associated with RA disease activity. PAI-1, VCAM and PECAM-1 play a role in the pathophysiology of RA, whereas PAI-1, E-selectin and P-selectin play a role in the pathophysiology of MetS.

AUTO1-0569
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

REDOX IMBALANCE IN SYSTEMIC LUPUS ERYTHEMATOSUS ARE ASSOCIATED WITH SEVERITY OF ILLNESS, AUTOIMMUNITY, INCREASED ADHESION MOLECULES AND TH1 AND TH17 IMMUNE SHIFT

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Background

This study investigated nitro-oxidative stress in patients with Systemic Lupus Erythematosus (SLE) in association with disease activity, immune-inflammatory biomarkers and adhesion molecules.

Method

204 patients with SLE and 256 healthy volunteers were enrolled in this case-control study, which measured nitro-oxidative stress biomarkers, including lipid peroxides (LOOH), advanced oxidation protein products (AOPP), nitric oxide metabolites (NOx), sulfhydryl (-SH) groups, products of DNA/RNA oxidative degradation; and total radical-trapping antioxidant parameter (TRAP). Also measured were antinuclear antibodies (ANA), antibodies against double-stranded DNA (dsDNA), plasma levels of diverse cytokines, C-reactive protein and adhesion molecules.

Results

LOOH ($p<0.001$) and AOPP ($p<0.001$) were significantly higher, while TRAP was significantly lower ($p<0.001$) in SLE patients than in controls. AOPP and LOOH were significantly and positively associated with SLEDAI scores, antinuclear antibodies and anti-dsDNA levels, whilst TRAP was significantly and inversely correlated with SLEDAI, ANA, and dsDNA antibody levels. There were significant positive associations between AOPP and LOOH and immune-inflammatory markers, indicating T helper (Th)-17 and Th1 bias and Th1+Th17/Th2 ratio ($p=.0.002$ and $p=0.001$ respectively). AOPP and LOOH (positively) and TRAP (inversely) were associated with adhesion molecule expression. A model predicting SLE was computed showing that, using LOOH, AOPP, NOx, adhesion molecules and body mass index, 94.2% of the patients were correctly classified with a specificity of 91.5%.

Conclusion

Increased nitro-oxidative stress takes part in the (auto) immune pathophysiology of SLE and modulates severity of illness and adhesion molecule expression.

AUTO1-0683
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

POST-TRANSLATIONAL MODIFICATIONS OF PROTEINS INDUCED BY AUTOPHAGY

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Background

Autophagy is an essential homeostatic and physiological process that promotes the "turnover" of proteins and organelles damaged in conditions of cellular stress.
We previously demonstrated that autophagy represents a key processing event creating a substrate for autoreactivity, which is involved in post-translational changes in proteins and generation of citrullinated peptides, recognized by the immune system in Rheumatoid Arthritis (RA).
In this study we analyze whether autophagy is involved in other post-translational changes that can generate autoantigens, focusing on carbamylation processes. Carbamylation is a nonenzymatic post-translational modification in which homocitrulline is generated by the reaction of cyanate with the primary amine of lysine residues; carbamylated peptides are reported to accumulate in several inflammation conditions.

Method

In vitro the role of autophagy in the generation of carbamylated proteins, and *ex vivo* the correlation between autophagy and carbamylated proteins in 30 naïve RA patients were evaluated. For autophagy induction, synoviocytes, fibroblasts and monocytes were treated with 5mM tunicamycin or 200nM rapamycin.

Results

Our results demonstrated that cells treated with tunicamycin or rapamycin showed a significant increase of carbamylated proteins. Immunoblotting and immunoprecipitation experiments identified vimentin as the main carbamylated protein. A correlation was found between autophagy and carbamylation levels in mononuclear cells of RA patients.

Conclusion

These data indicate that autophagy is able to induce *in vitro* carbamylation processes and *in vivo* appears to be related to an increase in carbamylation during RA. These observations introduce a new marker of disease that could contribute to more accurate clinical monitoring of patients.

AUTO1-0172
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ROLE OF FREE FATTY ACIDS IN THE DEVELOPMENT OF ORAL LICHEN PLANUS

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Background

Oral lichen planus (OLP) is a dermatological autoimmune disease of unknown etiology. We have chosen a group of patients having combination of OLP with hepatobiliary pathology and hypercholesterolemia with increased low-density lipoprotein (LDL) cholesterol level. It was demonstrated earlier that disorders in free fatty acids (FFA) composition may accompany the modification of LDL and affect development of several diseases. We suggested that patients having different forms of OLP also can have some blood FFA disbalance.

Method

We examined 15 OLP patients and 10 control subjects without any symptoms of OLP but having hepatobiliary disorders and hypercholesterolemia in their anamnesis. We studied the level of 19 types of long and medium chain FFAs in the blood serum by means of gas chromatographic analysis.

Results

We have demonstrated that the OLP patients had statistically significant increase of saturated lauric acid level (C12:0), p=0,04 in comparison to control subjects. As to the proportions between the particular types of fatty acids, significant changes of eicosapentaenoic (C20:5n3) and lauric acid (C12:0) concentration ratio, p=0,005, as well as eicosapentaenoic (C20:5n3) and linoleic acid (C18:2n6) concentration ratio, p=0,002, were observed. Changes in these FFA scores quantitatively depended on the form of OLP: the more expressed inflammatory reaction in the oral mucosa was, the larger the deviations from control group were.

Conclusion

So, serum FFA composition of OLP patients has specific pattern, different from control subjects and correlated with severity of disease progress. This correlation looks promising in GC methodology of lab diagnostics and prognosis of OLP development.

AUTO1-0805
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

STANDARDIZATION IN THE NOMENCLATURE USED FOR REPORTING ANTINUCLEAR ANTIBODIES IN A REFERENCE LABORATORY IN COLOMBIA

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Background

The implementation of the nomenclature suggested by the international consensus on patterns (ICAP) for the report of antinuclear antibodies, taking into account the discrepancies that currently exist between Colombian laboratories.
Antinuclear antibodies are a very useful test for the diagnosis of autoimmune rheumatic diseases. The standard gold methodology for its determination is the immunofluorescence assay, since different patterns can be observed that can indicate the antigenic target and the associated disease, however there are great differences in the results that are being issued by laboratories in the country, due to the variables associated with the methodology.

Method

400 samples were tested. The samples were tested in the automated HELIOS system and a manual reading was also done using an immunofluorescence microscope, the results were compared and classified according to the ICAP nomenclature. Positive samples were diluted to 1/2560, and the screening was started at 1/80 dilution. All the positive samples were confirmed with a second specific test.

Results

183 samples were negative and 217 were positive for ANA. The most representative percentages were for the negative pattern (AC-0), followed for the fine speckled pattern (AC-4) and for the homogeneous pattern (AC-1).

Conclusion

All the patterns observed in the substrate for ANA HEp-2 are described in the ICAP, classified according to the suggested tree simplifying in this way the report.

AUTO1-0632
MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES

ANTI-GM-CSF ANTIBODIES IN AUTO-IMMUNE DISEASES

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Background

Autoantibodies (Ab) to GM-CSF are associated with disseminated Crytococcus and Nocardia infections thus expanding the spectrum of associated diseases beyond pulmonary alveolar proteinosis.To our knowledge, no extensive study has been performed to evaluate the presence of these antibodies in auto-immune diseases.

Method

Healthy patients (HD) (n=84), patients with Crohn disease (CD) (n=24), systemic lupus erythematosus (SLE) (n=46), scleroderma (n=14), rheumatoid arthritis (RA) (n=13), vasculitis (n=14) and anti-phospholipid syndrome (APS) (n=37) sera were included. The tests were performed using an enzyme-linked immunosorbent assay (ELISA). We defined the cut-off of positivity as > 95th percentile from the OD values obtained with the 84 HD sera.

Results

Three out of 24 patients with CD exhibited anti-GM-CSF Ab and had a severe form of CD, as described on the litterature. None of the patients with RA and vasculitis were positives and only one with scleroderma had anti-GM-CSF antibodies above cut-off without gravity signs (Figure 1). Four out of 46 patients with SLE exhibited anti-GM-CSF Ab. The 4 SLE patients had a serious form of the disease. 3 of them had neurological damage. For 37 patients with an APS, the 5 patients with anti-GM-CSF Ab exhibited also an autoimmune disease.

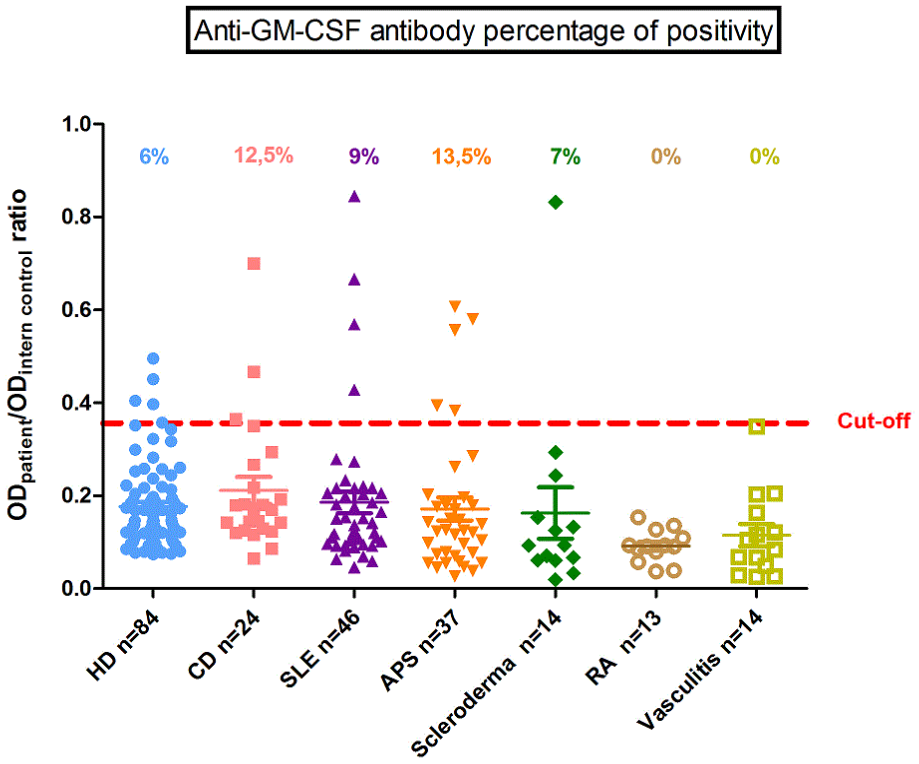

Figure 1: Pattern of distribution of anti -GM-CSF Ab among auto -immune diseases.
The red line indicates the c ut-off of positivity , defined as > 95th percentile from the value of 84 HD (cut -off = 0,356). Percentage of positivity is defined on top of each group (healthy donors (HD): 5 positive patients out of 84, 6% of positivity; Crohn disease (CD): 3 positive patients out of 24, 12.5% of positivity; systemic lupus erythematosus (SLE): 4 positive patients out of 46, 9% of positivity; anti -phospholipid synd rome (APS): 5 positive patients out of 37, 13.5% of positivity; scleroderma: 1 positive patients out of 14, 7% of positivity; rheumatoid arthritis (RA): 0 positive patient out of 13, 0% of positivity and vasculitis: 0 positive patient out of 14, 0% of posi tivity).

Conclusion

The absence of anti-GM-CSF in RA patients suggests a protective role of these Ab. By contrast, we found an association between neurological involvement in SLE patients and anti-GM-CSF Ab. Although, these results need to be confirmed, our study suggests that a monitoring of these antibodies could be useful to adapt immunosuppressive treatment in SLE patients.

AUTO1-0753
MIND-BODY INTERACTION IN AUTOIMMUNITY

AUTOIMMUNE DISEASES ASSOCIATED - CASE REPORT

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Background

Ankylosing spondylitis (AS) is a chronic, inflammatory and rheumatic disease from the group of spondyloarthropathies (SPAs), which primarily targets the sacroiliac joint and spine, and less frequently, the peripheral joints. It can also present with non-joint involvement. The disease frequently affects young adult males.

Method

We present the case of a 33-year-old patient suffering from ankylosing spondylitis, who came in for perioral paraesthesia and paresthesia on the right-hand side which started 5 days ago. Background disease began 5 years ago when, after a gastrointestinal infectious episode, the patient's knee arthritis was unresponsive to NSAID treatment but with favorable progression following treatment with sulfasalazine.

Results

Biologically, laboratory tests show moderate leukocytosis, moderate inflammatory syndrome, low sideremia. The neurological examination, supported by the outcome of the native cerebral MRI, raises the suspicion of multiple sclerosis, but does not exclude the diagnosis of toxocariasis. However, immunological markers for toxocariasis are negative. After the second MRI, with gadolinium constrast medium, according to the McDonald criteria, the diagnosis of multiple sclerosis is established.

Conclusion

Although the most common autoimmune diseases associated with ankylosing spondylitis are inflammatory bowel disease or psoriasis, unknown etiopathogenic mechanism and polymorphic symptomatology should always raise questions about any new emerging symptom, the diagnostic and therapeutic approach of these cases requiring imagistic support and interdisciplinary collaboration.

AUTO1-0687
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS

COMPARISON OF ANA IFI RESULTS WITH AN AUTOMATED MULTIPLEXED BEAD-BASED ANA SCREENING: THREE MONTHS LAB EXPERIENCE

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Background

The gold standard method for the ANA's determination is still the indirect inmunofluorescence (IFI). The early detection is very useful for the timely diagnosis of autoimmune disease. Recently, a multiplexed bead-based screening technology was applied to BioPlex 2200 for the determination of ENA. The aim of this work is to evaluate the agreement of the results with the two methods in three months of confrontation.

Method

In the period August-October, we analyzed 1337 samples, mean age 48 years (range 16-85), n. 939 females (70,2%). For IFI was used the Fluorescent IgG ANA-Ro Test Hep-2000, Immuno Concepts, Sacramento, USA (Alifax distribution in Italy); the reading was made in the Nikon Eclipse 50i microscope. All the samples were then processed with the BioPlex 2200 BioRad Laboratories, Hercules, USA, that uses high multiplexed technology, covering magnetic beads with cytoplasmic and nuclear antibodies.

Results

Of the 1337 patients, 298 (22,3%) were positive for different dilutions on the IFI test, and 269 (20,1%) were positive on the multiplex test. Among the former, the positivity is numerically greater, but all the discordant cases were mitochondrial, nucleolar, DFS-70 and some homogeneous, patterns not highlighted with BioPlex. On the other side, BioPlex found positiveness to Scl-70, Jo-1, Sm; such autoantibodies weren't always revealed by IFI and without multiplex methodology would have been misunderstood.

Conclusion

The BioPlex ANA test, excluding the samples with nucleus, mitochondrial, DFS-70 and homogeneous pattern, has shown a greater sensitivity than the Hep-2, in the almost positive patients for Scl-70, Jo-1, Sm, that would have been otherwise disregarded.

AUTO1-0380
MULTIPLEX DIAGNOSTIC TECHNIQUES AND CHIPS

EVALUATION OF A MICRO-ARRAY ASSAY FOR THE DETERMINATION OF ANTI-NUCLEAR/CELLULAR SPECIFICITIES RELATED TO SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

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Background

The objective of this work is to validate a new micro-assay for the analysis of antibody specificities related to SARDS.

Method

Anti-dsDNA, Ro60, Ro52, SSB, RNP, Sm, Scl-70, Jo-1 and CenpB Ab determinations by a micro-array assay (Zenit-Amidot, Menarini) were evaluated by comparison with a chemiluminescent assay (ZenitRA, Menarini) in sera from 222 SARD patients (100 SLE, 30 SSj, 46 SSc, 15 MCTD and 31 IIM) and in 120 healthy controls. Additional specificities contained in the micro-assay (PL-7, PL-12, Mi2, PM-Scl, RibP, Ku and PCNA) were also evaluated by comparing with blot results.

Results

A very good-good kappa coefficient agreement was observed between anti-Ro60 (0,888), Ro52 (0,825), SSB (0,812), RNP (0,764), Scl-70 (0,693), Jo-1 (0,827) and CenpB (0,898) assays. Anti-dsDNA assays displayed moderate agreement (0,451), the micro-array showing a higher diagnostic performance for SLE diagnosis (AUC: 0,835 *vs* 0,713). When considering the cut-offs corresponding to a 95% specificity, the kappa coefficient increased to good agreement (0,640). Anti-Sm determination showed the lowest agreement (0,291) mainly due to a lower sensitivity of the micro-array (4% *vs* 13%). When comparing with blot results, the micro-array displayed a good correlation for anti-PL7/PL12 (11/11), anti-Mi2 (6/6), anti-RibP (10/9) and anti-PM-Scl (6/7). The specificity of all these micro-array determinations was >98%. In addition, the micro-array detected previously confirmed reactivities in 2 anti-Ku y 2 anti-PCNA positive patients.

Conclusion

Overall, our results show a good performance of the Zenit-Amidot micro-assay in the assessment of anti-nuclear/cellular specificities related to SARDs. Nevertheless, the manufacturer should increase the sensitivity of the anti-Sm determination.

AUTO1-0179
NEW CYTOKINES AND ANTI-CYTOKINES

THE ROLE OF THE SMART RISK SCORE IN RHEUMATOID ARTHRITIS

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Background

The SMART risk score is a means of estimating the 10-year risk for myocardial infarction, stroke and global vascular death. Patients with rheumatoid arthritis (RA) are at increased risk of developing atherosclerosis and so it is important to detect cardiovascular (CV) involvement as early as possible.

Objective: to find a useful cut-off score for the CV follow-up of patients with RA and evaluate whether anti-TNF therapy can reduce the SMART risk.

Method

This was a retrospective study in which the SMART score algorithm was used to assess 25 patients with RA diagnosed on the basis of the 2010 ACR criteria (16F, 9M; mean age 55.71 ±7.06) and previously documented CV disease. The patients' CV profiles and blood parameters were evaluated before and after anti- TNF treatment, and the results were re-analysed using the SMART score to divide into four classes of low, low-intermediate, intermediate-high, and high risk.

Results

At baseline, 17% of the patients were classified as being low risk, 30% at low-intermediate risk, 45% at intermediate-high risk, and 8% at high risk. After 12-months of anti-TNF treatment, the corresponding percentages were 18%, 40%, 35% and 7%. Fisher's F test showed that there was no statistical difference in the best and worst risk classes, but a significant improvement in the intermediate classes as the patients at intermediate-high risk were reclassified as being at low-intermediate risk ($p<0.05$).

Conclusion

Anti-TNF therapy has a benefical effect on atherosclerotic vascular disease in RA patients as reflected by the change in SMART risk scores.

AUTO1-0713
NEW CYTOKINES AND ANTI-CYTOKINES

COMPARATIVE EFFICACY AND RETENTION RATE OF TOCILIZUMAB AND TNF INHIBITORS AS FIRST-LINE BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS: DATA FROM A MULTICENTRE OBSERVATIONAL REGISTRY

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Background

To retrospectively evaluate the 6- and 12-month comparative drug survival and remission rate of tocilizumab (TCZ) and TNF inhibitors (TNFis) as first bDMARD in a multicentre observational cohort of the LORHEN registry.

Method

RA patients treated with TCZ or a TNFi as first-line bDMARD from January 2009 to May 2016 and with at least 12-month follow-up were selected from the LORHEN registry. Six- and 12-month clinical remission rate was defined as achievement of DAS28-ESR <2.6. Drug persistence was calculated by Kaplan-Meier method. The comparison between treatment subgroups was performed by a chi-square test for remission data and by a log-rank test for drug survival. Moreover, DAS28-ESR remission rate has been corrected for drug discontinuation by using the LUNDEX formula

Results

The overall study population included 884 patients treated with TCZ (n=112) or TNFis (n=772; infliximab 59, adalimumab 238, etanercept 300, golimumab 86, certolizumab pegol 89). Baseline characteristics were similar in the two groups, with the exception of mean age (TCZ 57.1 vs TNFis 53.4 years; p=0.008). Clinical remission was achieved in overall 30.3% patients at 6 months (TCZ 54.4% vs TNFis 26.8%; p<0.001) and in 28.4% patients at 12 months (TCZ 46.6% vs TNFis 25.7%; p<0.001). Similar trends were observed after correction by LUNDEX at 6 (TCZ 45.8% vs TNFis 22.2%) and 12 months (TCZ 35.7% vs TNFis 17.8%).

Conclusion

Despite a similar 1-year retention rate, the proportion of patients achieving DAS28-ESR remission was significantly higher in TCZ treated group compared with TNFis, suggesting a deeper clinical response in patients receiving IL6 blockade.

AUTO1-0352
NEW CYTOKINES AND ANTI-CYTOKINES

IS IL-1α OVER-EXPRESSION A MARKER OF A SYSTEMIC AUTOINFLAMMATORY DISEASE (SAID) AT EARLY STAGE?

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Background

While IL-1beta release and functions are well defined, the exact role of IL-1alpha in autoinflammation has not been elucidated yet.

Method

We depict the case of a 26-year-old female with a history of chronic fatigue syndrome, fibromyalgia and recurrent fever attacks since childhood. During the disease course she developed cervical lymphadenopathy, asthenia and arthromyalgia. Genetic analysis showed an uncertain polymorphism for MVK and TNFRSF1A genes and laboratory data revealed a slight increase of IgD but normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and ferritin. IL-1alpha serum levels were consistently overexpressed while IL-1beta was normal. No hypermetabolic abnormalities were identified in the 18-FDG PET/MRI scan. The patient was treated with IV-immunoglobulin and steroids without significant benefit. Colchicine at the dosage of 1 mg/day was also ineffective.

Results

The clinical manifestations and genetic background presented by our patient are not linked to a specific SAID. In particular, IL-1alpha overexpression is not a common finding. IL-1alpha can be constitutively expressed in myeloid and non-myeloid cells and high levels can be found in patients with Systemic Lupus Erythematosus, Rheumatoid Arthritis and Systemic Sclerosis. The release of this cytokine can be inflammasome dependent or not, according to the trigger factor, assuming thus the existence of an alternative pathway by which inflammation may occur.

Conclusion

It should be understood if IL-1aplha overexpression, in the absence of acute phase proteins, may underlies an autoinflammatory condition and may be considered an early inflammation marker.

AUTO1-0162
NEW CYTOKINES AND ANTI-CYTOKINES

THE EFFECT OF THYMIC STROMAL LYMPHOPOIETIN (TSLP) IN CULTURED HUMAN PODOCYTES: AN INSIGHT INTO RENAL AUTOIMMUNITY

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[6]Hankuk University of Foreign Studies-, Division of Biomedical Engineering, Gyeonggi-do, Republic of Korea

Background

Thymic stromal lymphopoietin (TSLP) is a major cytokine that promotes TH2 responses and polyclonal B cell activation in various autoimmune inflammations such as eosinophilic esophagitis, psoriasis, allergy. However, it has rarely been studied in the field of renal autoimmunity and injury to podocytes, which is related to proteinuria.

Method

Podocytes were incubated with TSLP during the indicated time periods (6, 12, and 24 h) and whole-transcriptome RNA and microRNA (miRNA) sequencing was performed. Differentially expressed genes (DEGs) were analyzed.

Results

There were distinct changes between control vs TSLP condition. DEGs at 6h were 113 genes, DEGs at 12h were 19 genes and DEGs at 24h were 33 genes. There was a slight overlap between DEGs reponding TSLP with genes in PodNet which is a protein-protein interaction network of the podocyte and covers 315 genes and 223 interactions. Through the PPI interactions between DEGs, hub genes were identified such as POLE, SMAD4, HDAC9, SIRT1. Also, total of 23 differentially expressed microRNA were identified. (p value < 0.05) and their target DEG mRNAs were found using the microRNA Target Databases.

Conclusion

We identified meaningful DEGs in TSLP-induced podocytes and made a mRNA-miRNA gene network, which could be used in understanding the pathogenesis of proteinuria in various autoimmune diseases involving kidneys.

AUTO1-0312
NOVEL ASPECTS OF THERAPIES – GLUCOCORTICOIDS, BIOSIMILARS, CANNABIS, MUSIC

RHEUMATOID ARTHRITIS EXPERIENCE WITH TOCILIZUMAB

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Background

Rheumatoid arthritis (RA)is a chronic autoimmune inflammatory disease, characterized by joint destruction, and may have extra-articular manifestations. It affects about 0.7%of the world population, preferentially females.
Tocilizumab is a humanized monoclonal IgG1 anti-IL-6 receptor indicated in severe and/or rapidly envolving disease that has not previously been treated with DMARD,or in moderate to severe disease that does not respond or are intolerant to other therapies.
Objectives: 1.To characterize a population of RA patients treated with Tocilizumab; 2.To evaluate the efficacy ans side effects of Tocilizumab; 3.To study if Tocilizumab treated RA patients have statistically significant differences when compared with control group

Method

Retrospective and observational study between January 2013-May 2016.Consultation of clinical files, computer records of the consultation, analytical studies up to 2months before the start of therapy and 6months after.Statistical analysis with IBM® SPSS® Statistics software version 23of the variables age, sex, time evolution disease, VS, CRP, disease activity scale (DAS-28),blood count;Lipid profile

Results

We observed a total of 44patients; 67%female; Start age average was 42.7years;To the date of introduction of the drug, 30years and 4months was the average time of disease evolution;The most frequent lateral effect was neutropenia; one patient had hepatocellular dysfunction requiring reduction of the dose of the drug; one patient developed a cutaneous hypersensitivity reaction during the second infusion, body area<5%.No complication related to neoplasia.

Conclusion

Tocilizumab showed excellent efficacy in patients with moderate rheumatoid arthritis, with improvement of clinical criteria and reduction of functional limitation. Tocilizumab has a good safety profile that makes it safe and a good choice.

AUTO1-0918
NOVEL ASPECTS OF THERAPIES – GLUCOCORTICOIDS, BIOSIMILARS, CANNABIS, MUSIC

SWITCH FROM ETANERCEPT ORIGINATOR TO ETANERCEPT BIOSIMILAR: DATA FROM REAL LIFE

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Background

Biosimilars of antiTNF-α are now available for the treatment of arthritis. There are a lot of data about maintenance of clinical efficacy after switching from originator to biosimilar but also reports about flares and adverse events (AE). Controversies still exist due to ethical and economic reasons. We describe the disease activity trend after switching from etanercept originator (oETA) to its biosimilar (bETA) in a population of Turin, Piedmont, Italy. In this region switch to biosimilar is mandatory by law except in case of patients with history of allergy, off-label, psycological reasons, active disease that required different treatment.

Method

We switched 82 patients (M/F 33/49, mean age 59.65±11.5, duration of disease 17.56±10.3 years) in stable state of disease from oETA to bETA; 49 patients affected by RA, 24 by PsA, 10 by AS. The mean of duration of oETA and bETA treatment was respectively 129.2 and 6.2 months. We evaluated VAS-pain, Global-Health, CRP, number of swollen and tender joints, DAS28 for RA, DAPSA for PsA, HAQ and HAQ-S, BASDAI for AS patients.

Results

Differences of variables between oETA and bETA are summarized in table1. We didn't find any significant difference between oETA and bETA in order to efficacy. However 8 patients, 5 RA and 4 PsA(9.75%) discontinued bETA because arthritis flare(7) or AE(1).

Treatment	DAS28 RA	HAQ RA	DAPSA PsA	HAQ PsA	BASDAI SA	HAQ-S SA
oETA	2,61 (±0.92)	0.85 (±0.52)	8.15 (± 5.6)	0.88 (0.6)	2.88 (±2.6)	0.85 (±0.42)
bETA	2.68 (±1.21)	0.92 (±0.7)	11,66 (±9.63)	0.9 (±0.69)	2.7 (±2.16)	0.58 (±0.26)

Tab. 1 The analysis of variables between Etanercept originator (oETA) and Etanercept biosimilar (bETA)

Conclusion

Data about maintenance of efficacy and percentage of discontinuation were similar to the literature. We didn't find significant differences on efficacy after switching from originator to biosimilar.
However, considering the rate of flares and AE, further strong studies are required.

AUTO1-0512
NOVEL ASPECTS OF THERAPIES – GLUCOCORTICOIDS, BIOSIMILARS, CANNABIS, MUSIC

PROFILE OF AUTOIMMUNE RHEUMATOLOGICAL DISEASES IN CHILDREN IN A MEDICAL COLLEGE HOSPITAL

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Background

The prevalence of paediatric rheumatological illnesses vary, with JIA ranging from 0.07 to 10/1000 children and SLE from 0.4 to 0.6/100 000 children. Polyarticular JIA is the most common followed by SLE and enthesitis-related arthritis in India. The incidence is increasing due to awareness among pediatricians and better diagnostic armamentarium.

Method

All children with rheumatological symptoms were included over a year and their clinical, immunological profiles were reviewed. 43 patients from 278 referrals (OP and Inpatients) had rheumatological and rheumatology-like illnesses.

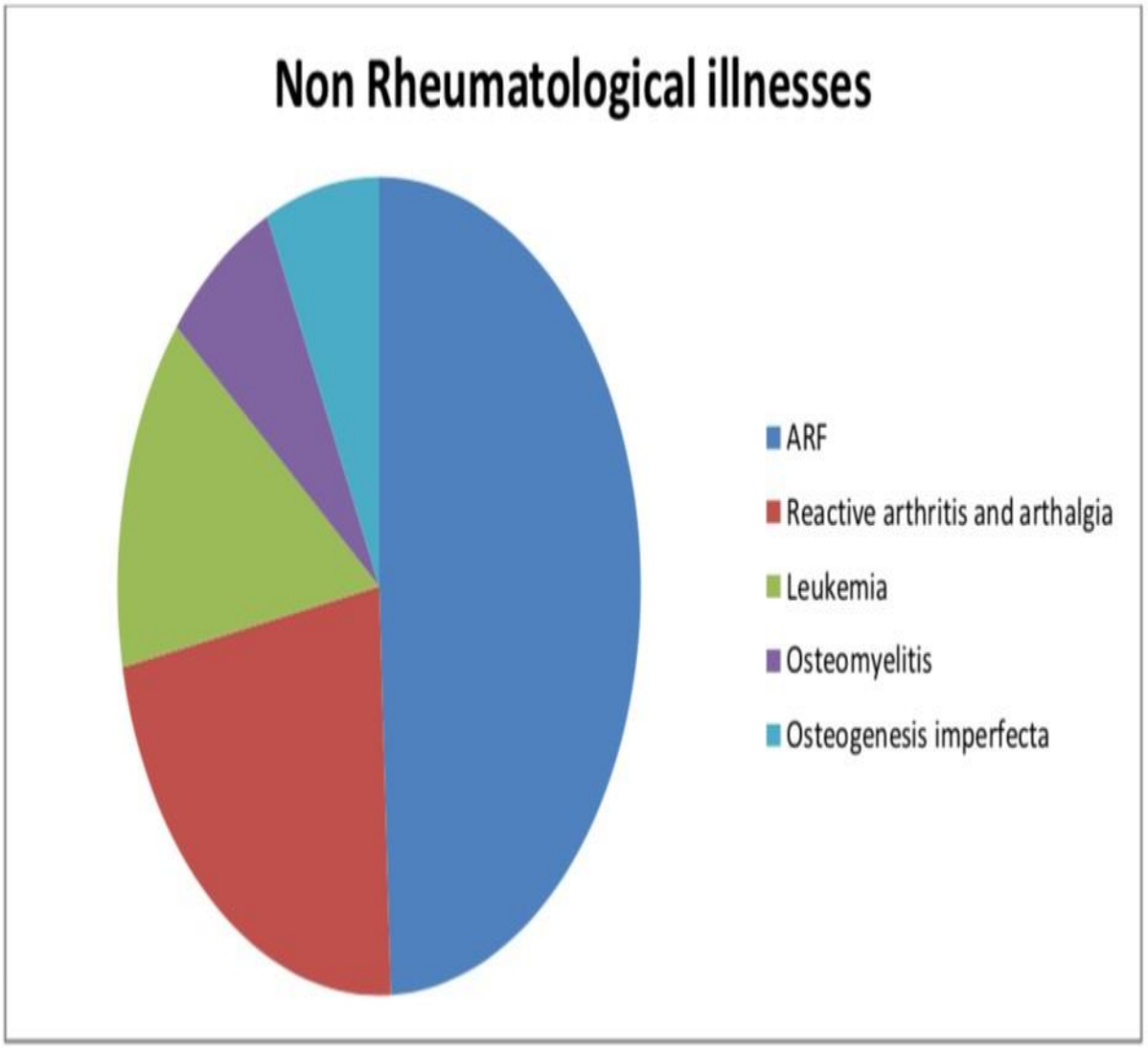
Results

Mean age of these children was 10.

29 patients had definite rheumatological diseases (table 1). M: F= 5:6

JIA	SLE	SSc	MCTD	Others
11	6	1	2	8

Others included CRMO, Kimura's, Fibromuscular dysplasia, B27 related arthritis, Protein S deficiency with young stroke, Juvenile polymyositis and autoimmune hepatitis. Rheumatology-like illnesses include acute rheumatic fever (undoubtedly the commonest),osteomyelitis, leukemia, septic arthritis


Non Rheumatological illnesses
ARF
Reactive arthritis and arthalgia
Leukemia
Osteomyelitis
Osteogenesis imperfecta

The immunological profile of rheumatological and non rheumatological illnesses:

ANA	7
dsDNA	4
RF	2
B27	1
p ANCA	1
ASO	7

Most patients had corticosteroids for induction of remission and specific DMARDs. Manifestations of rheumatic fever were treated with penicillin. JIA, SLE and Polymyositis were treated with cyclophosphamide, azathioprine or mycophenolate. All children are under regular follow-up and parents are happy with the coordinated care.

Conclusion

Autoimmune rheumatological diseases are common in girls than boys. Immunology may remain normal in paediatric rheumatological illnesses. We need to increase the awareness among the public and doctors as more children are identified with rheumatological ailments. Long term follow-up will help to understand the immunological diathesis in young children.

AUTO1-0651
NOVEL ASPECTS OF THERAPIES – GLUCOCORTICOIDS, BIOSIMILARS, CANNABIS, MUSIC

OXYGEN THERAPY OF INFLAMMATORY SKIN DISEASES

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Background

Traditionally, ROS have been implicated in the progression of various kinds of inflammatory diseases, including atopic dermatitis (AD) and psoriasis, but several opposing observations suggest the protective role of ROS in inflammatory diseases. Many inflammatory diseases were aggravated in rodents and human with lowered levels of ROS, such as Ncf-1$^{-/-}$, NOX2$^{-/-}$ mice and CGD patients, whereas attenuated in those with elevated levels of ROS, such as Gpx-1$^{-/-}$ and Prx II$^{-/-}$ mice, suggesting the anti-inflammatory role of ROS. In particular, the suppressive function of regulatory T cells (Tregs) seems to be closely linked to ROS level; *Ncf1$^{-/-}$* Tregs were hypofunctional, while Gpx1$^{-/-}$ Tregs were hyperfunctional.

Method

Based on this background, we investigated animal models of AD and psoriatic dermatitis (PD) in mice with elevated or lowered levels of ROS, such as Ncf-1$^{-/-}$and Gpx1$^{-/-}$ mice, or WT mice treated physically or chemically that may increase or decrease tissue levels of ROS; hyperbaric oxygen therapy or an oxygen-carrying chemical, perfluorodecalin increases, whereas antioxidants, such as N-acetylcysteine (NAC) or ascorbic acid decrease tissue ROS level.

Results

The results consistently showed appropriately elevated levels of ROS attenuated, whereas lowered levels of ROS aggravated, murine models of AD and PD. Correlation of Treg function with ROS level was also demonstrated in vitro by using DMNQ or NAC. In the present study, two molecules that may link ROS level and Treg function were investigated; Indoleamine 2,3-di-OXYGENASE and HYPOXIA-inducible factor-1α.

Conclusion

The results of the present study suggest the potential therapeutic effect of oxygen therapy for inflammatory skin diseases.

AUTO1-0725
NOVEL ASPECTS OF THERAPIES – GLUCOCORTICOIDS, BIOSIMILARS, CANNABIS, MUSIC

EFFECTIVENESS OF VARIOUS METHODS OF TREATMENT AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) IN CHILDREN

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Background

Goal to assess the prognostic factors of recurrent course and the effectiveness of therapy in children with AIHA

Method

The study included 18 patients with primary AIHA between the ages of 5 months to 12 years (median - 3.5 years), 8 of them boys and 9 girls.

Results

It was found that in 38.9% of patients the disease takes a relapsing course. In children with recurrent disease an initial level of CD4+CD8- lymphocytes in peripheral blood was significantly ($p<0.05$) lower than healthy children and children with acute course of the disease, and an initial level of CD19 + lymphocytes was higher. 77.7% of patients with childhood AIHA have response to the intravenous immunoglobulin (IVIG), but only 16.7% have a complete response to therapy. Younger age of the patient and an initial low level of CD3+HLA-DR+lymphocytes are favorable prognostic factors of response to therapy with IVIG. The probability of relapse after IVIG alone is 100%. Corticosteroids (GCS) can achieve a complete response in 66.6% of children. Combination therapy with corticosteroids and IVIG reduces the risk of relapse by 25%. Prognostic factors of response to therapy of GCS are red blood cell count, Coombs' test, CD4+/CD8+ index. Regardless of the type of first-line therapy long-term use of low-dose oral corticosteroids (45 + 15 days) after the main type of treatment significantly reduces the risk of relapse (55% vs. 78%) ($p = 0.004$).

Conclusion

Rituximab is an effective treatment of drug-resistant forms of AIHA, well tolerated by patients, and is not accompanied by serious systemic complications.

AUTO1-0075
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

THE THERAPEUTIC POTENTIALS AND THE IMMUNOMODULATION OF ENOLASE 1 (ENO1) BLOCKING ANTIBODY IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE) – ONE PRECLINICAL STUDY

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Background

Currently available information on plasminogen receptors, particularly their mechanisms of action and their roles in inflammatory, autoimmune and malignant disease had been addressed. *α*-Enolase (Enolase-1, ENO1) has been detected on the surface of hematopoietic cells such as monocytes, T cells and B cells, neuronal cells, and endothelial cells as a strong plasminogen receptor, modulating pericellular fibrinolytic activity. Enolase-1 (ENO1) upregulation or endogenous ENO1 antibody had been reported in diseases of childhood autoimmune retinopathy, acute inflamed lung disease, rheumatoid arthritis and autoimmune hepatitis. However, the exact immunopathologic role of ENO1 had not been proved in MS.

Method

Specific-blocking ENO1 antibody (ENO1 Ab, alpha-enolase specific antibody (Patent No: WO 2015095863 A3)) had been generated from Development Center for *Biotechnology* (DCB, Taiwan) and Technology transferring to HuniLife Biotech Co. and we proved this blocking ENO1 Ab as a therapeutic agent in experimental autoimmune encephalomyelitis (EAE) – represented an animal model of MS.

Results

We demonstrated ENO1Ab with protective effects in disease severity and ENO1 Ab group showed a significant upregulation of Tr1 (CD4+IL10+ T cells) and mild elevation of Tregs of splenocytes from EAE. We also displayed mice treated ENO1 Ab of EAE revealing dramatically repression of macrophage (CD11bF4/80) .

Conclusion

Thus, our study dissect the immunopathologic and inflammatory role of enolase 1 (ENO1) in EAE and develop further the therapeutic potential of ENO1 blocking antibody (ENO1 Ab).

AUTO1-0185
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

COMPARISON OF ELISA ASSAY FOR INFLIXMAB THERAPEUTIC MONITORING IN AUTOIMMUNE DISORDERS

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Background

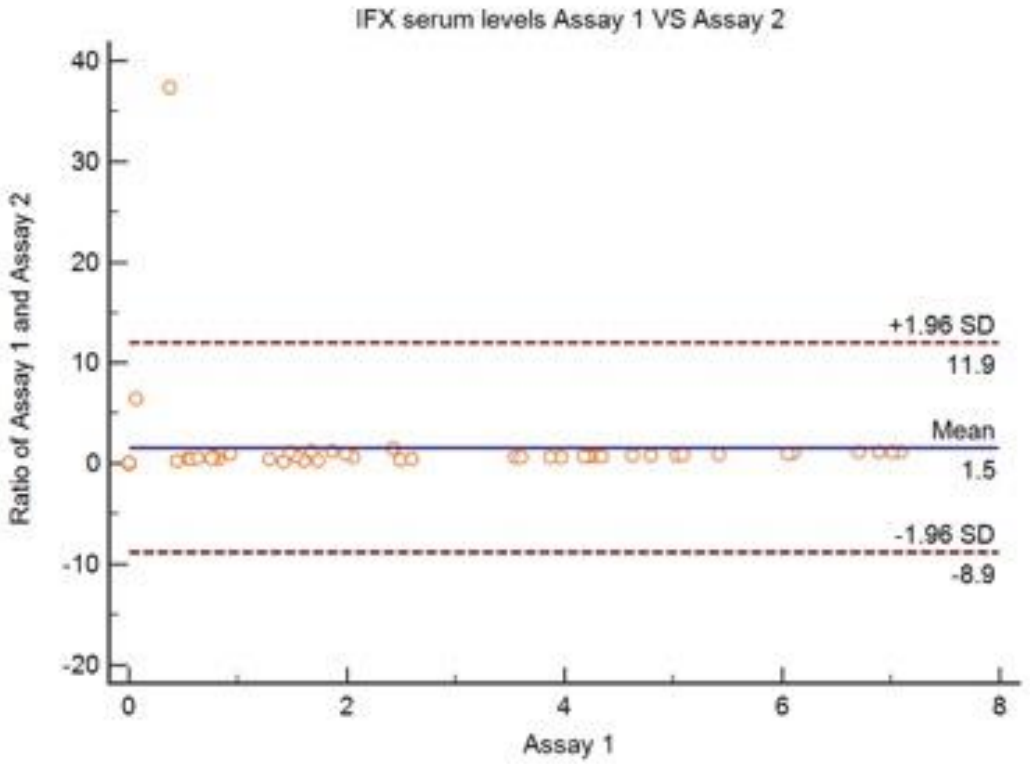
Infliximab (IFX) is one of the most important biological drug for the treatment of autoimmune diseases; however, despite the initial response rate, about 30% of patients show a lack of response or treatment failure because of the development of anti-Infliximab antibodies (anti-IFX Ab) that can influence IFX efficacy and pharmacokinetic. In the last years, different ELISA assays were developed for the detection of IFX serum levels and anti-IFX Ab in order to monitor IFX therapy and to prevent treatment failure.

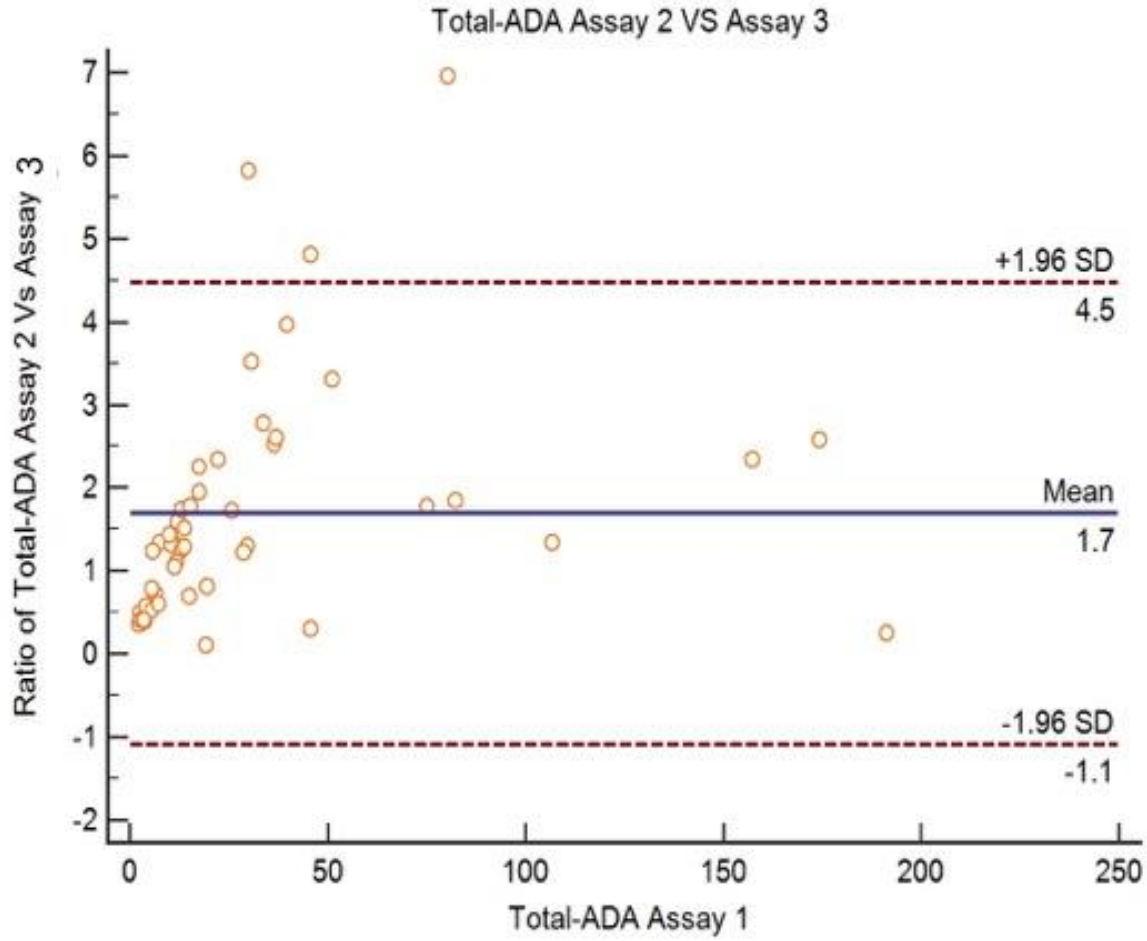
Method

We performed a comparison study of four different ELISA kits for IFX therapy in patients with autoimmune disorders, we compared results and we studied potential laboratory pitfalls. We analysed patients affected by gastroenterology and rheumatology disease using: Immunodiagnostik®, Tani Medical®, Matrix® and Theradiag® commercial available kit. We detected IFX serum levels and anti-IFX Ab and we compared the results with Bland-Altman statistic test.

Results

These methods seem to be concordant for IF serum levels detection (Figure 1) but we discovered significant differences in anti-IFX Ab results (Figure 2).





Conclusion We want to underline the need of standardization and harmonization between different ELISA tests and we invite laboratory and physician to a tight collaboration as to prevent laboratory mistakes.

AUTO1-0644
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

EARLY DETECTION OF ANTI-OSTEOPONTIN ANTIBODIES HAS A PROGNOSTIC VALUE FOR MULTIPLE SCLEROSIS PATIENTS AND VACCINATION INDUCING THEM IMPROVES EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Background

Osteopontin (OPN) is highly expressed in demyelinating lesions in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE). In EAE, treatment with anti-OPN antibodies ameliorates the disease. Anti-OPN auto-antibodies (autoAbs) are spontaneously produced during EAE, whereas their presence in MS is not known.

Method

Aim of the study was to search for anti-OPN autoAbs in the serum of MS patients, to correlate them with the disease course and, then, to recapitulate the human findings in EAE. We performed ELISA in the serum of 122 patients collected cross-sectionally, and 50 patients with relapsing-remitting (RR) disease collected at diagnosis and followed longitudinally for 10 years

Results

In the cross-sectional patients, the autoAb levels were higher in the RR patients than in the primary and secondary progressive patients and in the healthy controls, and were highest in the initial stages of the disease. In the longitudinal group, the levels at diagnosis directly correlated with the number of relapses during the following 10 years. In patients with active disease who underwent disease-modifying treatments, levels were higher than in untreated patients and inversely correlated with the MS severity score. In mice, vaccination with OPN conjugated with ovalbumin before EAE induction induced the production of anti-OPN antibodies and decreased the disease severity. The protective effect correlated with decreased T cell secretion of IL-17 and interferon –γ *ex vivo*.

Conclusion

In conclusion, antibodies to OPN may play a key role in MS evolution and EAE and novel strategies boosting their levels may be proposed for MS therapy.

AUTO1-0349
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

HLA-DR15 INHIBITION AS A TARGETED THERAPY IN EXPERIMENTAL AUTOIMMUNE ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

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Background

Anti-glomerular basement membrane (GBM) disease is a form of rapidly progressive glomerulonephritis. It has a strong association with the HLA-DR15 allele (odds ratio: 8.5), and the immunodominant T-cell epitope $\alpha3_{135\text{-}145}$ is restricted to HLA-DR15. A DR15-specific inhibitor, PV-267, has potential as a targeted therapy and may reduce the use of global immunosuppressants. This study aims to demonstrate that specific inhibition of HLA-DR15 attenuates autoreactivity to $\alpha3_{135\text{-}145}$ and disease.

Method

HLA-DR15 transgenic mice were used. Autoreactivity to $\alpha3_{135\text{-}145}$ was determined by immunising mice with $\alpha3_{135\text{-}145}$ at day 0 and administering PV-267 daily from day -1 to 10, then measuring recall responses *ex vivo*. Experimental autoimmune anti-GBM disease was induced by immunising mice with $\alpha3_{135\text{-}145}$ at days 0, 7, and 14; disease severity was assessed at day 42. PV-267 was tested in prevention and treatment models.

Results

Compared to the immune responses of vehicle controls, mice given PV-267 had reduced $\alpha3_{135\text{-}145}$-specific proliferation and fewer IFN-γ and IL-17A spots. In prevention, mice given PV-267 from day -1 were protected from disease, with reduced albuminuria, glomerular necrosis, IgG deposition, and cellular infiltrates. Autoimmunity was attenuated when mice were treated with PV-267 from day 21, with reduced functional and histological injury and fewer intrarenal $\alpha3_{135\text{-}145}$-specific $CD4^+$ T cells. Low dose treatment from day 28 did not attenuate disease, while high dose treatment from day 28 showed a trend to reduced glomerular injury.

Conclusion

HLA-DR15 inhibition attenuates autoimmunity in experimental autoimmune anti-GBM disease and demonstrates the potential for specific MHC inhibitors as a targeted therapy.

AUTO1-0385
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

REGULATION OF TYPE II COLLAGEN, MATRIX METALLOPROTEINASE-13 AND COX-2 EXPRESSION BY CALLUS EXTRACT FROM RESVERATROL-ENRICHED SYNTHETIC RICE VIA THE MAPK AND PI3K/AKT PATHWAYS IN CHONDROCYTES

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Background

Resveratrol is a natural polyphenolic, previous studies showed that many biological functions such as anti-inflammatory activity, antioxidant property, anti-infective and neuroprotective activities. The resveratrol transgenic rice line Iksan526 (IS526) has been beneficial health effects. However, the effects of IS526, an extract of resveratrol-enriched rice, on differentiation and inflammatory response in chondrocytes, and the mechanism underlying these effects are not clearly understood..

Method

1. IS526 callus cultures
2.Analysis for resveratrol contents of IS526 callus
3 MTT assay
4. PGE2 assay

Results

In this study, the cellular regulatory mechanisms of IS526, an extract of resveratrol-enriched rice, were examined in rabbit articular chondrocytes. Following IS526 treatment, the expression levels of proteins was detected via western blotting, Alcian blue staining, PGE_2 assay and Immunofluorescence staining. The results revealed that IS562-induced a loss of type II collagen and decreased sulfate proteoglycan levels in a dose- and time-dependent manner. In addition, IS526 caused cyclooxygenase (COX)-2, matrix metalloproteinase (MMP)-13 and PGE_2 production. Phosphorylation of ERK and p38 kinase were increased and phosphorylation of Akt was inhibited by IS526. Pharmacological inhibition of MMP-13 blocked the IS526-induced decrease in type II collagen level but COX-2 and PGE2 production were unchanged. Moreover, the inhibition of ERK-1/-2, p38 kinase and PI3K/Akt with PD98059 (PD), SB203580 (SB), and LY294002 (LY), suppressed IS526-induced COX-2 expression. Treatment with SB and LY, enhanced the suppression of type II collagen but PD rescued IS526-induced dedifferentiation

Conclusion

Thus, in rabbit articular chondrocytes, IS526 enhances inflammation through MAPK and PI3K/Akt signaling and MMP-regulated dedifferentiation via MMP-13 increase and downstream ERK-1/-2 and PI3K/Akt signaling.

AUTO1-0539
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

EFFICACY AND SAFETY OF TOCILIZUMAB IN GIANT CELL (TEMPORAL) ARTERITIS

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Background

Giant cell arteritis (GCA) is a chronic systemic vasculitis of large and medium sized vessel. It can involve the aorta and great vessels but is the targeting of muscular arteries from cranial branches of the aortic arch that gives rise to the most characteristic symptoms of GCA, with visual loss the most feared complication. Glucocorticoids are the mainstay of treatment but are associated with adverse events and with relapsed when tapered. Tocilizumab (TCZ), a humanized antihuman IL-6 antibody, has been used successfully as a treatment for GCA.

Method

This is an open case series in which two patients with GCA were treated with TCZ. We compare ITAS scores, erythrocyte sedimentation rate (ESR) and glucocorticoid dose pre-TCZ and post-TCZ.

Results

Both patients presented with visual loss, one of them after glucocorticoid was tapered. The two patients had a good clinical response to TCZ and ITASscore reduced to 1, with one patient partially recovered the vision. ESR reduced from an average of 79.5 to 3.5 and glucocorticoids dose reduced from an average dose of 55mg to 15mg. None patients had adverse events with TCZ.

Conclusion

We show the successful use of TCZ in refractory GCA. Our two patients had a good biochemical response to therapy and glucocorticoids were tapered without relapse of disease. TCZ was well tolerated without adverse events reported. One of our patients was evidence of recovered vision. Yet, the studies that evaluate patients with visual loss are lack and we need more data for evaluate the efficacy of TCZ in these patients.

AUTO1-0216
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

COMBINED TREATMENT WITH INTRAVENOUS IMMUNOGLOBULIN (IVIG) AND ZINC ASPARTATE AMELIORATES EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

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Background

Intravenous immunoglobulin (IVIG) application is widely used in replacement therapy of immunodeficiency disorders and in approved autoimmune indications. In addition, IVIG is used off-label for other autoimmune indications.

The trace element zinc is shown to play a regulatory role in the maintenance of immune functions. Based on several experimental data, a therapeutic zinc supplementation is under consideration as one possible option to treat T cell-mediated autoimmunity.

Method

The aim of the present study was to investigate the influence of IVIG (Octagam®, 10 mg/day), zinc aspartate (Unizink®, 30 µg/day) and the combined application of both preparations in the animal model of Multiple Sclerosis, the Experimental Autoimmune Encephalomyelitis (EAE).

Results

We observed that a therapeutic intraperitoneal application of zinc aspartate, given from day 11 to day 19, significantly reduced clinical signs during the relapsing remitting phase of EAE in SJL/J mice. In contrast, the IVIG preparation was capable of diminishing the severity of EAE only after preventive application from day 1 to day 10, but not in a therapeutic manner.

Interestingly, zinc aspartate increased the therapeutic effect of IVIG administration in the course of the EAE disease. The combined application of both IVIG and zinc aspartate preparations significantly reduced the severity of the disease during the acute and the relapsing remitting phase of the EAE.

Conclusion

Taken together, the data suggest that combined administration of IVIG and zinc aspartate may have beneficial effects on T cell-mediated autoimmune diseases, like MS. Further prospective studies should verify the possibility of controlled immunosuppressive IVIG and zinc therapy.

AUTO1-0353
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

Apremilast: a valuable option for the treatment of complex cases of psoriatic arthritis with or without cutaneous involvement.

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Background

Patients with psoriatic arthritis are often unresponsive to systemic treatments, including biologics. Apremilast is the first selective inhibitor of phosphodiesterase-4 approved by the US Food and Drug Administration in 2014 and by the European Commission in 2015 for the treatment of adult patients with active psoriatic arthritis and for patients with moderate to severe plaque psoriasis.

Method

In February 2017, Italian competent authority for drugs (AIFA) approved apremilast for the treatment of active psoriatic arthritis in patients who have inadequate response or are intolerant to at least two conventional DMARDs, and in which the biological drugs are contraindicated or not tolerated.

Results

Currently, only few Italian data are available.

We describe our experience with apremilast in complex clinical cases.

Conclusion

Apremilast can be considerated a valuable option for the treatment of complex cases of psoriatic arthritis with or without cutaneous involvement.

AUTO1-0377
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

BORTEZOMIB TREATMENT IN SEVERE REFRACTORY ANTI-NMDA RECEPTOR ENCEPHALITIS

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Background

A significant proportion of the patients with anti-NMDA receptor encephalitis failed to improve even after aggressive immunotherapy. It is proposed that long-lived plasma cell resistance to conventional immunotherapy is a cause of refractoriness. The proteasome inhibitor bortezomib is known to deplete plasma cells and the treatment effect of bortezomib in refractory patients was investigated.

Method

We consecutively enrolled patients with anti-NMDA receptor encephalitis who remained bedridden after the treatment with methylprednisolone, intravenous immunoglobulin, rituximab, and tocilizumab. Subcutaneous bortezomib was administered to all these severe refractory patients. Clinical response, functional recovery, and change in antibody titer in the cerebrospinal fluid was measured.

Results

For all the 5 patients enrolled, a degree of improved consciousness and/or decreased movement disorders was observed after 2 cycles of bortezomib. Two of the 4 patients who followed antibody titer in the cerebrospinal fluid showed a partial decline in antibody titer. However, none of the patients achieved functional recovery with modified Rankin Scale score (mRS) ≥4 after 6 months. Three patients advanced to cyclophosphamide with bortezomib and dexamethasone (CyBorD) regimen, which only resulted in additional adverse events without mRS improvement.

Conclusion

Although bortezomib showed the apparent short-term clinical responses for the severe refractory patients, the effect was limited and did not lead to long-term recovery.

AUTO1-0194
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

PHOSPHODIESTERASE AND PLATELET-ACTIVATING FACTOR AS THERAPEUTIC TARGETS FOR RHEUMATOID ARTHRITIS

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Background

This study evaluated the efficacy of the inhibition of tumor necrosis factor alpha (TNF-α) against rheumatoid arthritis (RA) through the inhibition of platelet-activating factor (PAF) or phosphodiesterase (PDE).

Method

Male rats with RA induced by collagen and adjuvant were chronically treated with rupatadine (RUP), a PAF antagonist, pentoxifylline (PTX), a nonspecific PDE inhibitor, and with rolipram (ROL) and thalidomide (TAL), two PDE4 specific inhibitors.

Results

RA presented increased TNF-α in plasma and interleukin (IL)-1β and IL-6 in synovial fluid (SF), histological alterations in the tibio-tarsal joint, as well as hind paw swelling, cyanosis, erythema, decreased lymphocyte number and increased basic aminopeptidase activity (APB) in synovial tissue (TS) and decreased APB in peripheral blood mononuclear cells. PTX and RUP did not present effects on the swelling. ROL and TAL decreased the swelling, as well as ameliorated histological aspects, plasma TNF-α and APB in TS. ROL or TAL alone did not alter IL-6, but recovered IL-1β in the SF. These effects were not different from those of the concomitant treatment with ROL+TAL, except that this combination also decreases the body mass.

Conclusion

It can be hypothesized that anti-RA action of TAL and ROL is due to the inhibition of TNF-α synthesis as consequence of PDE4 inhibition in its main cellular sources. The treatment with TAL alone emerges as an economical, simple and effective therapeutical alternative for RA, while the combination of ROL+TAL can be a viable option for RA sufferers with overweight or obesity.

Supported by FAPESP and CNPq.

AUTO1-0462
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

KALLIKREIN-KININ SYSTEM AND TYPE I INTERFERONS: A NOVEL REGULATORY AXIS IN LUPUS

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Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ damage. Interferon-α (IFN-α) is a central mediator in disease pathogenesis. Neuropsychiatric lupus (NPSLE) is one of the most common manifestations of human SLE often causing depression. Administration of IFN-α in patients with chronic viral infections or cancers causes depressive symptoms. The Kallikrein-Kinin System (KKS), comprised of kallikreins (klks), bradykinins (BKs) angiotensin converting enzyme (ACE) and other molecules, regulates many physiological processes, including inflammation and regulates brain functions. We have shown that myeloid dendritic cells (DCs) from Sle 1,2,3 (Sle) lupus-prone mouse model show a Type I IFN signature that predates disease onset.

Method

We used DCs from Sle and age-matched control C57BL/6 (B6) mice and treated with CpG (TLR9 ligand), R848 (TLR7 ligand) or recombinant IFN-α to induce Interferon Stimulated Genes (ISGs) and treated with molecules of the KKS. We used the MRL/lpr lupus-prone mouse model to check effects in NPSLE.

Results

Sle DCs exhibited decreased expression of *klk* genes compared to B6 DCs. TLR7/9 or IFN-α induced ISG expression was markedly diminished by BKs, klk1 (tissue klk) or captopril (ACE inhibitor) in B6 mice. BKs also suppressed ISGs induced by CpG *in vivo* in B6 and Sle mice. Exposing MRL/lpr mice to IFN-α increased depressive-like behavior, decreased klk expression, and enhanced ACE expression in the brain. ACE activity decreases BK levels; administering captopril decreased ISG expression in brain and kidney.

Conclusion

The KKS-IFN cross-regulatory pathway may provide a rationale for therapeutic use of KKS molecules for treatment of systemic and neurolupus.

AUTO1-0394
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

ANTI-INFLAMMATORY miRNAS- OPPORTUNITIES FOR INFLAMMATORY DISEASES TREATMENT

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Background

Inflammation is a complicated biological and pathophysiological cascade of responses to infections and injuries, and inflammatory mechanisms are closely related to many diseases. The magnitude, the complicated network of pro- and anti-inflammatory factors, and the direction of the inflammatory response impact on the development and progression of a variety of disorders. Available clinical treatment strategies often target the symptoms and not the causes of inflammatory disease and may often be ineffective. Since the onset and termination of inflammation are crucial to prevent tissue damage, a range of mechanisms has evolved in nature to regulate the process including negative and positive feedback loops. In this regard, microRNAs (miRNAs) have emerged as key gene regulators to control inflammation, and it is speculated that they are fine-tune signaling regulators in order to allow for proper resolution and prevent uncontrolled progress of inflammatory reactions.

Method

In this review, we discuss recent findings related to significant roles of miRNAs in immune regulation and potential utility of these molecules as novel anti-inflammatory agents to treat inflammatory diseases.

Results

We have identified a set of unique miRNAs with anti-inflammatory properties and their regulatory pathways. The expression levels of these miRNAs may offer promising diagnostic value and severity prediction of different inflammatory diseases since miRNAs are stable in human blood, detectable with high sensitivity/specificity methods and measurable via miRNA microarrays and qRT-PCR arrays.

Conclusion

Although miRNA-based therapy will have limitations, we anticipate that it will be considered in future strategies aimed at diagnosing and treating acute and chronic inflammatory disorders.

AUTO1-0114
NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY

APAF1 PLAYS A NEGATIVE REGULATORY ROLE IN T CELL RESPONSES BY SUPPRESSING ACTIVATION OF ANTIGEN-STIMULATED T CELLS

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Background

Apaf1 is a critical component of the apoptosome and initiates apoptosis downstream mitochondrial damages. Although the importance of Apaf1 in embryonic development was shown, the role of Apaf1 in immune responses, especially T cell responses, has yet to be elucidated.

Method

We generated T cell-specific Apaf1-deficient mice (Lck-*Cre-Apaf1*$^{f/f}$ mice) and examined the antigen-specific delayed-type hypersensitivity (DTH).

Results

Lck-*Cre-Apaf1*$^{f/f}$ mice exhibited exacerbation of DTH responses as compared with Apaf1-sufficient control mice. In Lck-*Cre-Apaf1*$^{f/f}$ mice, antigen-specific T cells proliferated more, and produced more inflammatory cytokines than control T cells. Apaf1-deficient T cells from antigen-immunized mice showed higher percentages of activation phenotypes upon restimulation *in vitro*. Apaf1-deficient T cells from naive (non-immunized) mice also showed higher proliferation activity and cytokine production over control cells. The impact of Apaf1-deficiency in T cells, however, was not restored by a pan-caspase inhibitor, suggesting that the role of Apaf1 in T cell responses was caspase-independent/non-apoptotic.

Conclusion

These data collectively demonstrated that Apaf1 is a negative regulator of T cell responses and implicated Apaf1 as a potential target for immunosuppressive drug discovery.

AUTO1-0165
PEPTIDES AND AUTOIMMUNE DISEASES: DIAGNOSTICS AND THERAPY

DIFFERENTIAL EXPRESSION AND CO-LOCALIZATION OF S100A7/JAB1 IN PSORIASIS: A PRELIMINARY STUDY IN PSORIATIC PATIENTS AND IN S100A7 CRISPR-ACTIVATED HUMAN KERATINOCYTE CELL CULTURE

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Background

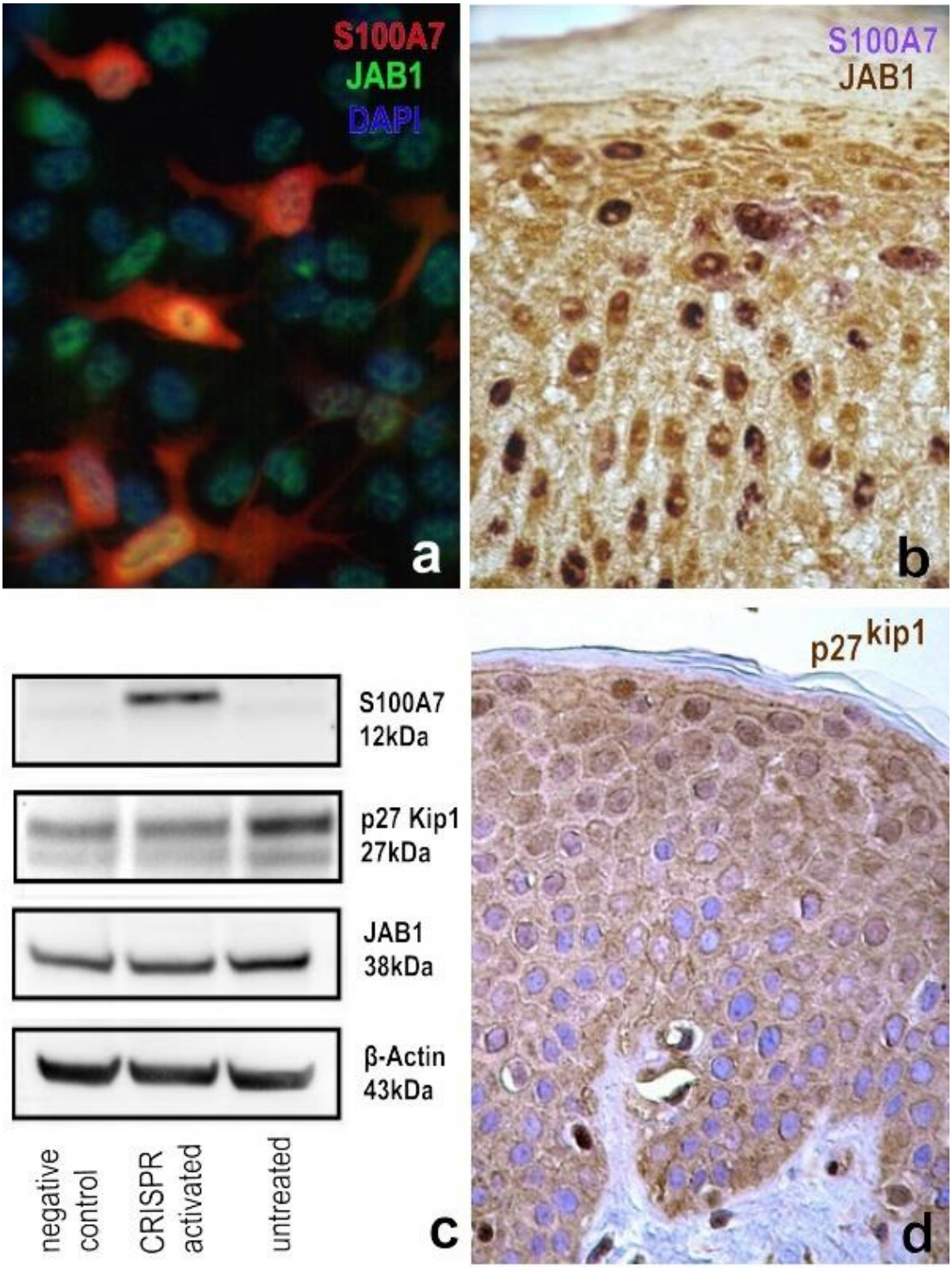
S100A7 is a member of the S100 family, EF-hand calcium-binding signalling proteins localized in epithelial cells. S100A7 has been found to be involved in antimicrobial defence, inflammation and immunomodulation. Binding site between S100A7 and JAB1, a transcription co-factor that stabilizes c-Jun, has been identified and characterized. In the nucleus, JAB1 is also a part of the COP9 signalosome protein complex that downregulates the cell cycle inhibitor $p27^{Kip1}$, as shown in epithelial cancers. The purpose of this study was to investigate S100A7, JAB1, $p27^{Kip1}$ expression in psoriatic skin samples and in normal human keratinocyte cells, transfected with psoriasin CRISPR activation plasmid.

Method

Expression levels and distribution of these proteins were analysed by immunohistochemistry, immunocytochemistry, immunofluorescence and western blot.

Results

Our preliminary results showed that, after transfection, S100A7 translocated into nuclei of normal keratinocytes and co-localized with JAB1 (figure a). Similarly, S100A7 co-localized with JAB1 in keratinocyte nuclei from psoriatic patients (figure b). Moreover, JAB1 and $p27^{Kip1}$ expression did not seem to be influenced by S100A7 overexpression (figure c). However, in skin samples from healthy subjects, p27kip1 was more expressed at cytoplasmic level compared to psoriatic subjects. Some nuclei of the spinous layer of unlesional psoriatic skin samples were immunostained for $p27^{Kip1}$ (figure d).



Conclusion

In conclusion, our study showed that, overexpression of s100A7 is accompanied by its translocation into the nucleus, with a possible interaction with JAB1. $p27^{Kip1}$ expression resulted to be decreased only in an inflammatory condition such as psoriasis, thus suggesting that overexpression of S100A7 alone may not suffice to downregulate $p27^{Kip1}$.

AUTO1-0471
PEPTIDES AND AUTOIMMUNE DISEASES: DIAGNOSTICS AND THERAPY

AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS (PAP) SUCCESSFULLY TREATED WITH NEBULIZED RECOMBINANT GM-CSF

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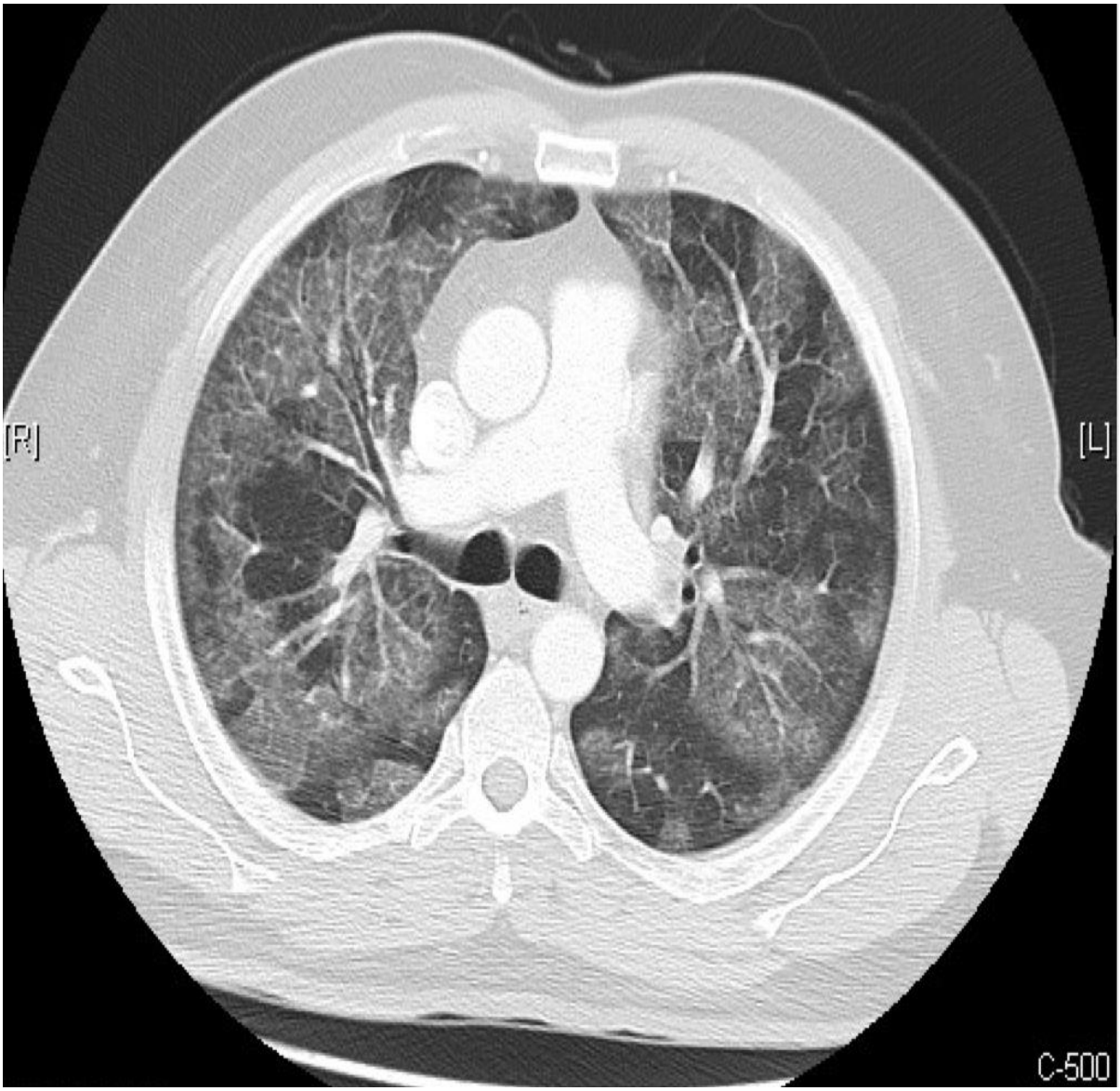
Background

Introduction: Pulmonary alveolar proteinosis is a rare lung disease characterized by the alveolar accumulation of surfactant components that course with variable clinical manifestations. The detection of anti-GM-CSF antibodies suggest that acquired PAP have an autoimmune pathogenesis. The etiology of the antibodies is unknown.

Method



Case: The patient had nonproductive cough and progressive dyspnea on exertion for 12 months.

A 47-year-old male, with a 19 pack-year history of cigarette smoking, working in an environment without inhalation of microparticles. Take care of two parakeets for eight years. Obesity type I and dyslipidemia.

Allergy to grass, olive tree and mites.

The physical examination was normal, except crackles involving half the way up in both lung fields.

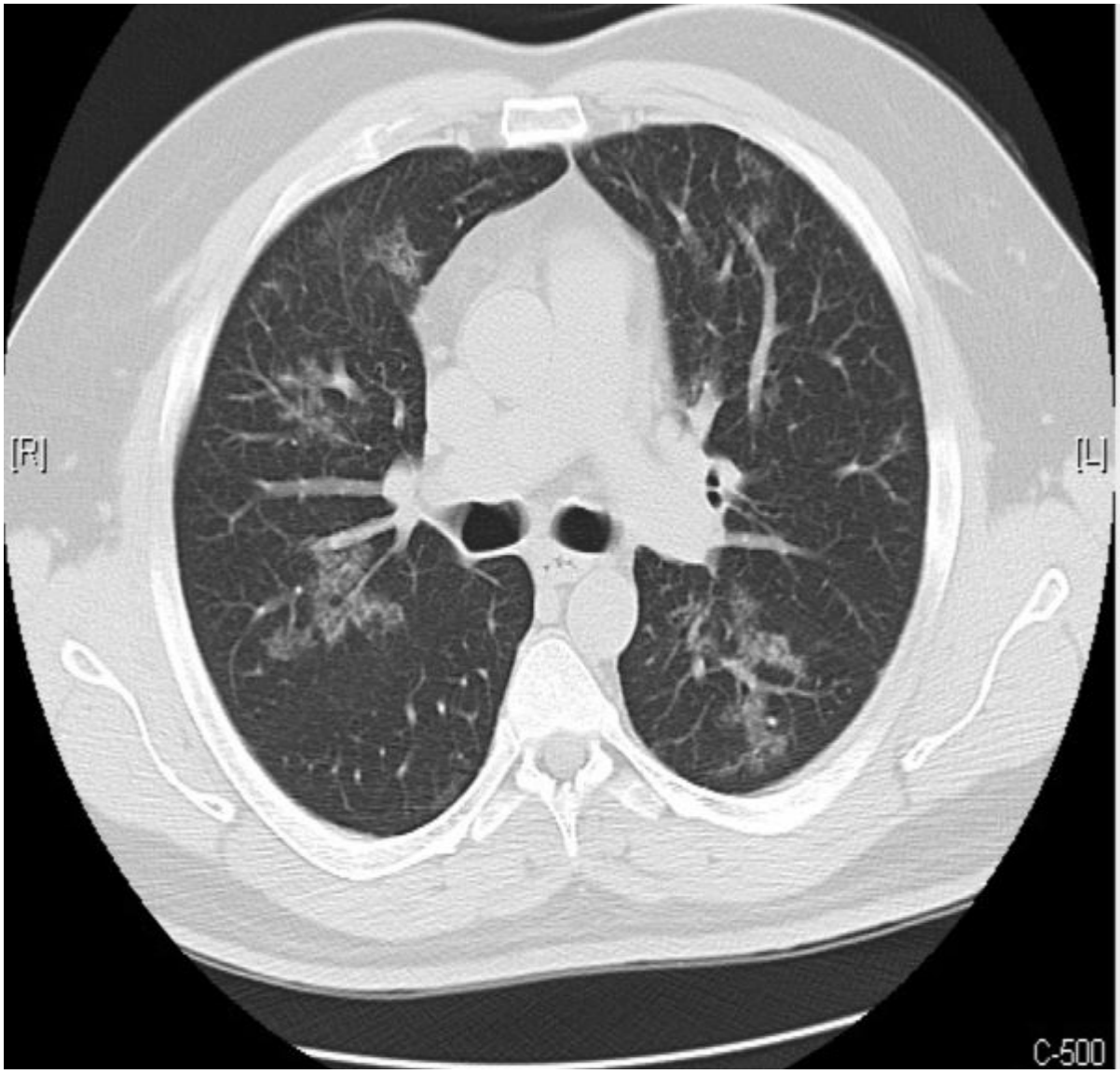
Results: Laboratory analyses: hemogram and routine chemistry results were normal. Immunoglobulines: IgG 999 mg/dL [600-1700], IgM 65.5 mg/dL [40-230], IgA 263 mg/dL [70-400]. Autoimmunity: ANA, ANCA negatives. Antibodies anti GM-CSF 15.6 mg/mL (normal <5mg/mL).

Chest radiograph: Bilateral alveolar opacities in middle and upper fields.

High resolution computed tomography (HRCT): bilateral ground-glass opacification in upper and middle fields, "crazy-paving" pattern. (Image 1)

Transbronchial lung biopsy: PAS-positive material

Results



Treatment: After eight months of treatment with GM-CSF via inhalational the patient is free of symptoms, the lung function and the control HRCT (Image 2) are markedly improved.

Conclusion

Conclusions: Although whole lung lavage is the most widely accepted and effective form of treatment, in our case the patient has been treated with GM-CSF via inhalational with spectacular symptomatic and radiographic improvement.

AUTO1-0232
PEPTIDES AND AUTOIMMUNE DISEASES: DIAGNOSTICS AND THERAPY

THE RATIO OF GALECTIN-3/GALECTIN-9 IN SERUM COULD REFLECT DISEASE ACTIVITIES AND CHANGE OF ACTIVITIES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory multiple arthritis, that is driven by autoreactive T cell mediated diverse cytokines. Galectin has been reported to play immune modulatory roles in diverse inflammatory diseases. We investigated whether the serum concentrations of galectin-3 and galectin-9 were associated with disease activity in patients with RA.

Method

We measured serum concentrations of galectin-9 and galectin-3 from RA patients and matched controls. Serum concentrations of galectin-9 and galectin-3 were compared with RA activities. We also compared serum levels of several cytokines with galectins and RA activities. Patients with active RA were followed-up after starting medications. Follow-up serum galectin-9 and -3 concentrations and their ratio were compared with those at the initial visits.

Results

Serum concentrations of galectin-9 and galectin-3 were elevated in RA patients, as compared to controls. The serum galectin-9 level was inversely correlated with the change of activities in patients with RA, although it did not show the clear association with disease activities. The serum galectin-3 level was significantly associated with disease activities such as ESR, CRP and DAS28ESR and was decreased after controlling disease activities. Finally, the ratio of galectin-3/galectin-9 was positively correlated with disease activities and the change of activities. The serum IFN-γ level showed an association with RA activities, as well as soluble galectin-3 and the galectin-3/galetin-9 ratio.

Conclusion

The serum galectin-9 and galectin-3 were amplified in patients with RA compared with healthy controls, and the ratio of galectin-3/galectin-9 in serum was associated with disease activities and change of activities in patients with RA.

AUTO1-1060
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

AN IMMUNE COMPLICATION OF STATIN THERAPY

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Background

Statins are amongst the most prescribed drugs worldwide and are generally safe. Nonetheless, in recent years, a very rare form of immune-mediated statin-associated myopathy has been described.

Method

Report of a case vignette.

Results

A 67 year-old female with hypertension and dyslipidemia treated with atenolol 100mg and simvastatin 20mg for the last 5 years presented with a 1-month history of asthenia and proximal myalgias with proximal tetraparesis. On examination there was a grade 3/5 proximal tetraparesis. Laboratory evaluation showed a raised CK (4338 IU/L) and ESR (60mm/h); ANA, ENA and anti-SRP were all negative but the anti-HMG-CoA reductase were positive. The muscle MRI and EMG revealed signs of symmetric and active myositis on the proximal muscles of the upper and lower limbs; the deltoid biopsy showed a necrotizing myopathy. There was no interstitial lung disease but the pulmonary function tests showed low maximal inspiratory and expiratory pressures. A diagnosis of statin-associated autoimmune myopathy was made, the statin was stopped and the patient was treated with three IV pulses of methylprednisolone 500mg followed by oral prednisolone 40mg/day (0,7mg/kg) with a marked improvement. During the steroid taper there was an early relapse leading to a transient rise on the steroid dose and introduction of oral methotrexate. At 1-year of follow-up the patient is on complete remission whilst on 2.5mg of prednisolone and 15mg of methotrexate.

Conclusion

The clinicians should be aware of statin-associated autoimmune myopathy because a good outcome often implicates a prompt diagnosis, discontinuing the drug, introducing immunosuppressive therapy and not reintroducing statins.

AUTO1-0557
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

VISFATIN IN MULTIPLE SCLEROSIS

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Background

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects 2.3 million people worldwide. The pathogenesis of MS might involve factors that link the immune system with the metabolic status. Obesity negatively influences disease progress and treatment response in MS. Adipose tissue secretes many biologically active substances named adipokines. Visfatin, one of adipokine, possesses various properties including proliferative, anti-apoptotic and pro-inflammatory activity.

Method

Subjects
Thirty-nine naïve to treatment MS patients (23 lean and 16 overweight or obese) and 42 controls (29 lean and 13 overweight or obese) age-matched.

Methods
Visfatin, IL-6, TNF-alpha, IL-10 and C-reactive protein concentrations were measured in peripheral blood.

Results

In group of overweight/obese MS individuals we found significantly higher visfatin concentration (9.48 ng/ml ± 3.09 vs. 7.01 ng/ml ± 3.3 in controls; $p< 0.05$). No differences were observed in IL-6, TNF-alpha, IL-10 and C-reactive protein concentrations between MS and control group.
Visfatin, IL-6, TNF-alpha and C-reactive protein values were comparable between lean MS patients and their healthy counterparts. IL-10 values were higher in non-obese MS individuals than in the controls (4.31 pg/ml ± 3.28 vs. 2.24 pg/ml ± 1.55; $p<0.05$).
There were no marked differences in visfatin concentration between multiple sclerosis subgroups.

Conclusion

Our results suggest that visfatin might serve as a link between adipose tissue and pathological processes in multiple sclerosis.

AUTO1-0520
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

CLINICAL CHARACTERISTICS OF PATIENTS WITH ANTI-OJ AUTOANTIBODIES

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Background

Anti-OJ (anti-isoleucyl-tRNA synthetase) autoantibodies are anti-aminoacyl-tRNA synthetase (ARS) that have been found in approximatly 5% of patients with polymyositis/dermatomyositis (PM/DM). Previous studies suggested that anti-OJ may distinguish a subtype of ARS syndrome that is closely associated with interstitial lung disease (ILD) than with myositis. Our main goal is to evaluate the clinical characteristics of anti-OJ positive patients.

Method

Anti-OJ-positive patients were consecutively selected from the database of adult patients to whom myositis-specific and myositis-associated antibodies had been requested, from January 2012 to November 2017. Anti–OJ was identified via immunoblotting, (Euroimmun®). The results were defined as weakly (+), moderately (++) or strongly (+++) by two independent clinical pathologists.

Results

The presence of autoantibodies was evaluated in 489 patients with clinical suspicion of PM/DM. Anti-OJ was identified in 4 patients (0.81%). Two man and two women with a mean ±SD age of 58±13 (min: 47 years; max: 81 years). In 2 patients, the anti-OJ was strongly detected, in one was moderately and in the fourth it was weakly positive. In three patients there was coexistence of other autoantibodies (anti-SRP, anti-Ku and anti-Mi-2). None of the patients had clinical evidence of ILD. Two patients had history of proximal muscle weakness and increased concentrations of creatine kinase. The two other did not have any complaints but were hepatitis B core and surface antibodies positive.

Conclusion

In our sample, the anti-OJ autoantibodies were not associated to ILD. Two patients presented characteristics of PM/DM and the two others presented hepatitis B antibodies.

AUTO1-0411
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

ROLE OF MIR-150 IN AUTOIMMUNE MYASTHENIA GRAVIS

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Background

Acquired myasthenia gravis (MG) is mainly mediated by auto-antibodies against the acetylcholine receptor at the neuromuscular junction. In early-onset MG, the thymus is often characterized by B-cell infiltrations leading to ectopic germinal center (GC) development. microRNAs are small non-coding RNAs that regulate protein expression through direct interactions with mRNAs. They are involved in many physiological and pathophysiological processes, including autoimmune diseases.

We previously demonstrated that miR-150-5p is upregulated in the serum of MG patients, and is significantly downregulated after thymectomy in correlation with disease improvement *(Punga et al. 2014)*. Beyond its role as a biomarker, this study aimed at investigating further the role of miR-150 in the physiopathology of MG.**Method**

We showed that miR-150 was overexpressed in the thymus of MG patients with numerous GCs and decreased when patients were under corticoid treatment. The thymic levels of miR-150 were correlated with the expression of the B-cell marker CD19, and *in situ* hybridizations showed that thymic overexpression of miR-150 was due to its high expression in naive B cells located in the mantle zone of GCs.

Results

We also demonstrated that high serum levels of miR-150 in MG could have a functional effect on peripheral blood mononuclear cells (PBMCs) by acting on target genes. Indeed, *in vitro* treatment of PBMCs with miR-150 or an antagomiR-150 decreased or increased, respectively, the expression of its major target, c-Myb.

Conclusion

Altogether, our data demonstrates that miR-150 could play a role in MG both at the thymic level and in periphery by modulating target gene expression.

AUTO1-0719
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

LATE-ONSET CERVICO-BRACHIAL MYOSITIS WITH ANTI-KU ANTIBODIES

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Background

Cervico-brachial myositis is a rare entity, characterized by involvement of the neck and upper limbs, with relative conservation of the lower extremities. The differentiation from muscular dystrophies, myelopathies, brachial plex lesions, and other neuropathies or myopathies is not always simple.

Method

A 68-year male patient, with no statin exposure and denying chronic alcohol consumption, was assessed for a progressive, insidious weakening of the upper limbs and neck muscles.

Results

Examination revealed deltoid hypotrophy, scapulo-humeral anterior rotation and chest flattening. A cervical MRI and shoulder ultrasonography found only degenerative changes. Deltoid muscle elastography suggested a dense, „fibrotic" pattern. The analyses showed minimal inflammation (ESR 28 mm/h, CRP 1.1 mg/dl, normal <0.6 mg/dl) and a mild elevation of the liver enzymes (TGO 88, TGP 72, normal <40 IU/dl), and creatine kinase (463, normal< 308 IU/L). The viral hepatitis tests, complement fractions, rheumatoid factor, cryoglobulins, immunoglobulins and serum protein electrophoresis were non-contributive. However, a low antinuclear antibodies titer (1/160 speckled) and positive anti-Ku antibodies in immunoblot were noted. EMG was myopathic and the biopsy revealed perimysial and perivascular inflammation, with no amyloid deposition. He slowly improved on corticosteroids, azathioprine, antioxidants and vitamin D.

Conclusion

Cervico-brachial myositis could be a peculiar clinical variant of myositis, mimicking a late-onset dystrophy. Detection of immune abnormalities may help identify a potentially curable disease.

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Khadlikar SV, Gupta N, Yadav RS: Cervico-brachial polymyositis. J Clin Neuromuscul Dis 2014; 16(2): 59-68.

AUTO1-0730
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

HIKER'S FEET IN INFLAMMATORY MYOPATHIES: THREE CASES

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Background

"Hikers's feet" is a newly-described cutaneous sign in inflammatory myopathies, the equivalent of "mechanic's hands" in antisynthetase syndrome, depicting hyperkeratosis of the toes and plantar surface of the feet.

Method

We retrospectively reviewed for the presence of plantar skin changes, the records of patients with inflammatory myopathies presenting over the last 2 year in our center. In all cases with hyperkeratosis, fungal and viral skin infections and palmo-plantar psoriasis were ruled out by the dermatologist. The presence of sacroiliitis, plantar fasciitis and Achilles tendons enlargement were also searched for and recorded.

Results

We identified 3 cases of "hiker's feet" in inflammatory myopathies, all females, two with polymyositis (one with anti-Jo-1, one with PL7/PL-12) and one in dermatomyositis with anti-Ro-52 positivity. All the three patients fulfilled the clinical criteria for antisynthetase syndrome (polyarthritis, myositis, Raynaud's fenomenon, mechanic's hands, interstitial pneumonitis and fever). All had hyperkeratosis and crackling of the hands, mainly of the 2nd finger, of the sole and toes; none had sacroiliitis or Achilles entesopathy.

Conclusion

"Hiker's feet" should be searched for when suspecting an inflammatory myopathy. Also, as plantar hyperkeratosis may mislead to a spondylarthritis, creatine kinase should be routinely checked in these patients.

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Cox JT, Gulloti DM, Mecoli CA, Lahouti AH, Albayda J, Paik J et al: „Hiker's feet": a novel cutaneous finding in the inflammatory myopathy. Clin Rheumatol 2017; 36(7):1683-6.

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AUTO1-0375
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

EVIDENCE OF SUBCLINICAL CARDIAC DYSFUNCTION IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background

Patients with idiopathic inflammatory myopathies (IIM) have high chances to develop subclinical heart disease: it occurs in up to 50% of them and it is difficult to detect through conventional imaging. This study aimed to investigate the usefulness of global longitudinal strain (GLS) measurement to detect a subclinical systolic ventricular dysfunction in patients with IIM.

Method

We enrolled 28 patients with IIM and 28 matched controls in a 1:1 ratio. We measured the standard variables for both left (LV) and right ventricle (RV) systolic and diastolic function plus the speckle-tracking GLS. We also researched a possible correlation between GLS and muscle strength, disease activity, cardiovascular risk factors, and other organ systems involvement.

Results

Standard variables of systolic and diastolic dysfunction were similar between patients and controls. GLS was significantly lower in patients when compared with controls for both LV (–18.7 ± 4.2% vs –21.2 ± 2.1%, p = 0.006) and RV (–19.3 ± 6.3% vs –22.5 ± 3.8%, p = 0.033). Patients with IIM had a 4.9-fold increased risk for impaired left GLS, which involved usually anterior, anterior-septal and lateral wall. Patients with IIM had a 3.4-fold increased risk for impaired right GLS with the basal segment of the free RV wall most frequently involved. Muscle strength, disease activity, damage and duration, other organ system involvement and previous treatment were not associated with reduced GLS.

Conclusion

Subclinical systolic impairment is common in patients with IIM. In this context, GLS assessment is a non-invasive, precocious and useful tool.

AUTO1-0369
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

DROPPED HEAD SYNDROME: A RARE MANIFESTATION OF SCLEROMYOSITIS

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Background

Dropped head syndrome (DHS) is characterized by severe neck extensor muscles weakness. It can be the first clinical manifestation of several neuromuscular diseases, like Miastenia Gravis and Idiopathic Inflammatory Myopathies (IIM). Scleromyositis is a rare condition characterized by an overlap between Systemic Sclerosis and IIM. We here describe three patients with Scleromyositis who presented with DHS.

Method

Three women came to our attention for neck muscles weakness, dysphagia and Raynaud's phenomenon. On physical examination, patients had microstomia, sclerodactily and mild hypostenia of neck extensor and proximal arm muscles. Nailfold capillaroscopy showed a scleroderma pattern. Chest x-ray demonstrated interstitial thickening, while pulmonary function tests were normal. Blood tests revealed the rise of creatinphosphokinase (CK> 500 U/l) and lactate dehydrogenase (LDH>350 U/l). Anti-PM/Scl antibodies were positive in two patients. Finally, electromyography and muscle biopsy confirm the diagnosis of IIM.

Results

The first patient received steroid therapy and tocilizumab, as she also suffered from rheumatoid arthritis. Due to a recent history of cancer, the second patient did not receive an immunosuppressive therapy. She thus was treated with intravenous immunoglobulin, followed by maintenance therapy with subcutaneous immunoglobulin. The last patient promptly improved with steroid therapy, whereby a maintenance therapy with subcutaneous immunoglobulins was set. After four months, all patients improved, with reduction of muscular weakness and dysphagia. Moreover, CPK and LDH returned to normal values.

Conclusion

DHS can be the first clinical manifestation of Scleromyositis. A complex multidisciplinary approach is necessary to recognize and treat this rare condition.

AUTO1-0393
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

RESPONSE OF DYSPHAGIA TO SUBCUTANEOUS IMMUNOGLOBULIN IN INFLAMMATORY IDIOPATHIC MYOPATHIES

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Background

Polymyositis and dermatomyositis are the most frequent idiopathic inflammatory myopathies (IIM), characterized by a systemic inflammation which involves especially skeletal muscle. Oesophageal involvement in course of IIM is frequently described and affects mostly the proximal segment of oesophagus, with dysphagia to solids and liquids and risk of aspiration pneumonia. The aim of our study was to evaluate the response of dysphagia to subcutaneous immunoglobulin (20%SCIg) therapy in patients with IIM.

Method

We report data of 14 patients, 7 with PM (6 females e 1 male) and 7 with DM (all females), diagnosed according Bohan and Peter's criteria, presenting with dysphagia. All patients were treated with 20%SCIg (0,1-0,2 g/kg). We assessed the response to treatment, in terms of improvement, stability or worsening of symptoms linked to dysphagia.

Results

After a mean follow-up of 18 months we observed an improvement of dysphagia in 12 patients on 14 (5/7 with PM and 7/7 with DM), meanwhile it remained stable in the others two cases (with PM). No worsening of oesophageal symptoms were observed.

Conclusion

SCIg therapy is useful in patients with IIM and, accordingly to our data, SCIg is particularly effective, not only for the muscular involvement, but also for the oesophageal one.

AUTO1-0538
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

INCREASED HERPES VIRUS AND VARICELLA ZOSTER VIRUS ANTIBODIES INDEX IN THE CEREBROSPINAL FLUID OF MULTIPLE SCLEROSIS PATIENTS WITH NEGATIVE OLIGOCLONAL BANDS

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Background

Varicella Zoster Virus (VZV) and Herpes Virus (HSV) are proposed to play a role in the pathogenesis of Multiple Sclerosis. The purpose of the study was to evaluate the presence of VZV and HSV antibodies in patients with Multiple Sclerosis (MS) and Clinically Isolated Syndrome (CIS) both in serum and cerebrospinal fluid.

Method

94 patients with Multiple Sclerosis were studied. Fifty seven patients were relapsing remitting MS (RRMS) and 37 patients had clinically isolated syndrome (CIS) and two with Radiologically Isolated Syndrome. The presence of VZV and HSV antibodies was tested in the serum and cerebrospinal fluid (CSF) of all patients

Results

HSV IgG and VZV IgG were detected at increased levels in serum in patients with RRMS. In CSF, values >1.5 were considered to be indicative of intrathecal IgG production against the respective pathogen. IgG index of HSV and VZV in RRMS was marginally positive in low levels. Increased HSV IgG index in CSF (>2) was found in 12/57 patients with RRMS. 5/12 (41%) had negative oligoclonal bands while from RRMS patients with negative HSV and VZV index in CSF only 4/45 (9%) had negative oligoclonal bands, p=0.01. Five patients with CIS had increased HSV IgG index. 3/5 CIS patients and 7/12 RRMS patients with positive HSV IgG index in CSF were in relapse with gadolinium enhancement in MRI.

Conclusion

The positivity of HSV and VZV IgM antibodies in CSF of MS patients without any sign of infection, might support a role of immune response against viruses in disease pathogenesis

AUTO1-0581
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

CLINICAL FEATURES OF IDIOPATHIC INFLAMMATORY MYOPATHIES: AN OBSERVATIONAL STUDY

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Background

Idiopathic inflammatory myopathies are a group of heterogeneous muscle disorders characterized by progressive muscle weakness and elevated muscle enzymes. Although muscle weakness stands as a hallmark, other systemic clinical features have been described in literature. We aimed at describing the epidemiological factors, prevalence and characteristics of this clinical features, as well as our laboratory findings, in patients diagnosed with either polymyositis (PM), dermatomyositis (DM) or inclusion body myositis (IBM).

Method

We performed an observational cross-sectional study based on the consultation of clinical records of 75 patients followed-up at Centro Hospitalar do Porto. Statistical analysis was performed using the SPSS software.

Results

As it has been described in previous studies, we observed a high prevalence of the female gender on the studied population (82,7%). There were 20 patients diagnosed with PM (26,7%), 53 with DM (70,7%) and only 2 with IBM (2,7%). The mean age of diagnosis was 46,1±16,7 years and the mean age of onset of symptoms was 44,5±16,5 years. There was a median (interquartile range) delay of 5 months (3-12) between the onset of symptoms and the diagnosis. Throughout the follow-up, various systemic manifestations were reported, affecting the musculoskeletal system in 48% of patients, the cardiac system in 30,7%, the pulmonary system in 54,7% and the gastrointestinal system in 49,3% of patients.

Conclusion

Although this muscle disorder might affect only the muscle function, extramuscular manifestations are frequent and can contribute to disability and impaired quality of life. More efforts should be made in order to raise awareness to a prompt diagnosis.

AUTO1-0533
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

PHENOTYPE OF ANTI-JO1 POSITIVE PATIENTS IS NOT AFFECTED BY HLA-DRB1*0301 GENOTYPE, BUT SEROLOGICAL AND CLINICAL FEATURES AT DIAGNOSIS ARE PREDICTIVE MARKERS OF MORE SEVERE DISEASE

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Background

The aim of this study was to determine the clinical, serological and genetic features of anti-Jo1 positive antisynthetase patients followed by a Hungarian single center to find prognostic markers, which can predict disease phenotype and progress.

Method

It was a retrospective study using clinical database of 49 anti Jo1 positive patients. The presence of anti-Jo-1 antibody was detected by immunoblot and ELISA. DNA was genotyped using a commercial sequence-specific oligonucleotide kit.

Results

100% of patients exhibited myositis, 73% interstitial lung disease, 88% arthritis, 65% Raynaud's phenomenon, 43% fever, 33% mechanic's hand and 12% dysphagia. We could detect significant correlation between anti-Jo-1 titer and the CK and CRP level at disease onset (CK: R=0.328; p=0.003; CRP: R=0.374; p=0.016) and during disease course (CK: R=0.497; p<0.001; CRP: R=0.325; p<0.001). HLA DRB1*03 positivity was present in 68.96% of the patients, where the CK level at diagnosis was significantly lower compared to the HLA DRB1*03 negative patients (2816.30 vs. 5969.44 U/l; p=0.04). HLA DQA1*0501-DQB1*0201 haplotype was found in 58.62% of the patients, but no significant correlation was found regarding to any clinical or laboratory features. Higher CRP, ESR level, anti-SSA and RF positivity and the presence of fever at diagnosis indicated a more severe disease course, requiring aggressive treatment within anti-Jo1 positive patients.

Conclusion

The phenotype of the disease was not different in HLA-DRB1*0301 positive or negative patients who had the anti-Jo1 antibody; however anti-Jo1 level might reflect disease activity. Distinct laboratory and clinical parameters at diagnosis could be considered as prognostic markers.

AUTO1-0090
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

VITAMIN D DEFICIENCY IS ASSOCIATED WITH DISABILITY AND DISEASE PROGRESSION IN MULTIPLE SCLEROSIS PATIENTS INDEPENDENTLY OF OXIDATIVE AND NITROSATIVE STRESS

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Background

The aim of this study was to assess vitamin D status in patients with multiple sclerosis (MS) and to evaluate whether it was associated with oxidative and nitrosative stress (O&NS) markers and disability.

Method

This study included 137 patients with MS and 218 healthy controls. The markers evaluated were serum levels of 25-hydroxyvitamin D, lipid hydroperoxides, advanced oxidation protein products (AOPP), nitric oxide metabolites (NOx), and total radical-trapping antioxidant parameter TRAP/UA.

Results

Patients with 25(OH)D <20 ng/mL showed higher Expanded Disability Status Scale (EDSS) scores (p=0.016), Multiple Sclerosis Severity Score (MSSS) scores (p=0.005) and lower AOPP (p=0.046) than those with 25(OH)D ≥ 20 ng/mL. After the binary logistic regression analyses, EDSS and MSSS remained significantly associated with vitamin D deficiency. We showed that lower levels of 25(OH)D were associated with higher EDSS and MSSS independently of variables such as O&NS, age, sex, body mass index, ethnicity, MS therapy, use of interferon beta, and clinical forms of MS (odds ratio: 1.380, 95% confidence interval 1.030-1.843, p=0.031). Moreover, the study showed an association between serum levels of 25(OH)D and EDSS (r2=0.115, p=0.002), demonstrating that 25(OH)D may contribute with 11.5% of increase in EDSS.

Conclusion

Our results suggest that vitamin D deficiency may be considered one of the predictors of the disability in MS patients, independently of their redox status and influence the progression of disability in MS.

AUTO1-0291
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

CONTRIBUTION OF MYOSITIS SPECIFIC AUTOANTIBODIES ASSESSMENT FOR THE DIAGNOSIS OF ATYPICAL JUVENILE DERMATOMYOSITIS: A CASE REPORT

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Background

Juvenile dermatomyositis (JDM) is a rare and heterogeneous childhood autoimmune disease. Early diagnosis and initiation of treatment have been shown to reduce complications and improve patient outcome.

Method

Here we report the case of a 7-years old girl presenting with a 4-years history of inferior limbs, back and hands' pains associated with cutaneous eruptions. Skin involvement was characterized by hands edema, metacarpophalangeal palmar erythema and photosensitivity. The child had a remitting and relapsing course, but without complete remission between the flare-ups. Before admission in our institution, lots of explorations were found normal, including creatine kinase quantitation, antinuclear antibodies detection, inferior limbs MRI and electromyogram. At the time of admission, symptoms were asthenia, muscle weakness (Childhood Myositis Assessment Scale score 42/51) and myalgia, without active skin disease. According to Bohan and Peter criteria, she had a possible JDM.

Results

Despite absence of antinuclear antibody by immunofluorescence on HEp-2 cells, we tested for myositis specific antibodies (MSAs) by line blotting, revealing a strong positivity for anti-TIF1gamma autoantibodies without any positivity of other MSA or myositis associated autoantibodies. Anti-TIF1gamma autoantibodies were retrospectively highlighted on previous sera of the patient. Confirmation by adressable laser bead immunoassay is in progress. Thus JDM diagnosis was retained and appropriate treatment started.

Conclusion

MSAs occur exclusively in children with myositis and have never been found in children with genetic muscle disease in the absence of a coexistent inflammatory myopathy. Our case highlights the need to investigate MSAs, even in patients without all patterns of abnormalities, avoiding JDM diagnosis delay.

AUTO1-0371
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

DETECTION OF INTRATHECAL IMMUNOGLOBULIN SYNTHESIS: A RAPID AND EFFICIENT APPROACH USING A COMBINATION OF KAPPA FREE LIGHT CHAIN INDEX AND OLIGOCLONAL BANDS

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Background

The gold standard for the detection of intrathecally synthesized IgG (iIgG), a diagnostic feature in multiple sclerosis, is the identification of oligoclonal IgG bands (OCB) in the cerebrospinal fluid (CSF) by isoelectric focusing. Recently, the nephelometric determination of Kappa free light chain (FLC) concentration in CSF and serum has been described to assess iIgG.

Method

We retrospectively analyzed 599 CSF/serum pairs and compared absolute Kappa-FLC CSF and Index values to OCB.

Results

Using a cutoff of 0.4 mg/l for absolute Kappa-FLC and 12 for Kappa-FLC-Index, the sensitivities were 94.6% (absolute) and 85.0% (Index) when compared to OCB. The specificities were 85.6% and 97.9% respectively. The Kappa-FLC-Index showed good performance in detecting iIgG. To discriminate multiple sclerosis patients as well as for an OCB-independent approach for the assessment of iIgG an optimal cutoff on the basis of clinical data needs to be defined.

We propose a complementary use of the Kappa-FLC-Index and OCB for the analysis of iIgG. Setting the cutoff to >2.3 or >14.3 the sensitivity or, correspondingly, the specificity in relation to OCB increases to >99%. Thus, with an initial screening for Kappa-FLC-Index 67.4% of all samples (≤2.3 and >14.3) could directly be reported negative or positive for iIgG based solely on the Kappa-FLC-Index. Samples with a Kappa-FLC Index between 2.3 and 14.3 (32.6%) would further be assessed by isoelectric focusing for OCB.**Conclusion**

With this approach the laborious and cost-intensive testing by isoelectric focusing can be minimized to a third of all samples analyzed for iIgG.

AUTO1-0013
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

EFFECT OF TREATMENT ON CLINICAL AND LABORATORY PARAMETERS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background

Multiple sclerosis (MS) is a complex inflammatory, demyelinating and neurodegenerative disease with a heterogeneous pathology and clinical outcomes. The majority of the treatments for MS are long term mainly suppressing the immune system however, such immune-suppressants pose increased risks for infections, metabolic disorders and cancer

Method

50 MS patients classified according to the 2010 McDonald criteria and 50 control subjects (CS), adjusted by age and sex, were included in this study. Treatment were classified as: No treatment, disease-modifying drugs (IFN-β1a, IFN-β1b and glatiramer acetate), low-efficacy treatment (cyclophosphamide and azathioprine) and high-efficacy treatment (teriflunomide, dimethyl fumarate and rituximab). Hematic cytometry was measured by automatic hematology analyzer; and serum levels of metabolic parameters were determined by spectrophotometer methods. Very low density lipoproteins (VLDL) levels were calculated by Friedwald equation. The data was analyzed with STATA v12 software and $p<0.05$ was reported as statistically significant

Results

We found a significant difference between the different treatments with ESR ($p=0.031$), platelets ($p=0.011$), band neutrophils ($p=0.001$), mean corpuscular hemoglobin ($p= 0.002$), mean corpuscular hemoglobin concentration ($p=0.004$) and low-density lipoproteins ($p=0.012$)

Conclusion

Our study indicated that treatment strategy have impact on clinical and laboratory levels in MS

AUTO1-0987
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

DERMATOMYOSITIS WITH CALCINOSIS, ULCERATION AND AUTOANTIBODIES TO NUCLEAR MATRIX PROTEIN (NXP-2) (ANTI-MJ)

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Background

Autoimmune myositis is a syndrome, caracterized by involvement of the cellular and humoral immune systems in skeletal muscle pathology, immunogenetic modulation and the presence of autoantibodies (Abs) (myositis-specific and myositis-associated Abs) in the serum of some patients. A new Abs, called anti-MJ Abs reported in juvenile dermatomyositis (JDM) patients, and it was associated with severe muscle weakness, polyarthritis, joint contractures and interstitial vasculitis. Anti-MJ Abs reported in JDM is also found in adult polymyositis/ dermatomyositis (PM/DM), as it is also unclear whether anti-MJ Abs has the same clinical significance as JDM.

Method

We present a clinical case of 39-years old female patient with distinct subset of dermatomyositis, caracterized by typical skin lesions (heliotropic rash, Gottrons papules), marced calcinosis complicated with “ulcerations”, without internal organ damage and positive anti-MJ Abs.

Results

. The soft-tissue calcification confirmed on the x-ray of the pelvis. It was made a skin biopsy, which showed acantosis, sparing mononuclear cellular infiltrates in the dermis, without accumulation of hyalinised collagen. By reason of the positive antinuclear antibodies (ANA) 1:640 (normal<1:80), it was tested many antibodies against different nuclear and cytoplasmic antigens. It was found positive anti-NXP2 Abs. The anti-NXP2 Abs is uncommon in adults (1.6% of patients). It seems to be more frequent in JDM.

Conclusion

. Further studies with larger cohorts of patients with anti-MJ antibodies are required for better understanding of clinical associations, etiopathogenesis and mechanisms of disease development. .

AUTO1-0489
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

EVALUATION OF A NOVEL BEAD BASED ASSAY FOR THE DETECTION OF AUTOANTIBODIES IN INFLAMMATORY IDIOPATHIC MYOPATHIES IN A US REFERENCE LABORATORY

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Background

Myositis specific antibodies (MSA) represent not only important diagnostic tools, but also help to stratify patients in to subsets with particular clinical features, treatment responses and disease outcome. These antibodies even have the potential to be used in classification criteria. Consequently, standardization of MSA is of high importance. Many laboratories rely on immunoprecipitation (IP) for the detection of MSA which however, will suffer regulatory challenges in the future. Therefore, reliable alternatives are mandatory. Recently significant variation between IP and line immunoassays (LIA) for the detection of MSA and MAA were observed. Therefore, we aimed to analyze the agreement of a novel method for the detection of MSA with routine methods used in a US reference laboratory.

Method

A total of 89 samples submitted to a US reference laboratory for testing of MSA antibodies were included. All samples were tested using novel bead based immunoassays (Inova Diagnostics, research use only) in parallel to the reference methods. The analysis focused on antibodies to HMGCR, Tif-1y, NXP-2, MDA-5, Mi-2, SRP, PL-7 and PL-12.

Results

Good agreements between the novel bead based immunoassays and the reference methods were found. The results are summarized in the table below:

Antibody	Reference methods	Agreement PPA/NPA/TPA	Kappa	AUC (95% CI)
HMGCR	ELISA	98.5/87.5/96.3	0.88 (0.75-1.00)	1.00
Tif-1y	ELISA	100.0/90.0/97.8	0.93 (0.80-1.00)	0.99 (0.97-1.01)
NXP-2	ELISA	100.0/90.0/97.8	0.93 (0.80-1.00)	0.99 (0.97-1.01)
MDA-5	ELISA	97.1/90.0/95.6	0.93 (0.80-1.00)	0.91 (0.77-1.04)
Mi-2	IP	96.2/90.0/94.4	0.86 (0.68-1.00)	0.92 (0.77-1.00)
SRP	IP	100.0/100.0/100.0	1.00 (1.00-1.00)	1.00 (1.00-1.00)
PL-7	IP	100.0/90.0/97.6	0.93 (0.80-1.00)	0.98 (0.95-1.02)
PL-12	IP	100.0/85.7/97.0	0.90 (0.72-1.00)	0.92 (0.77-1.08)

Conclusion

Good correlation between the novel IIM assays and routine methods used in a large reference laboratory were observed.

AUTO1-0500
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

EVALUATION OF NOVEL IMMUNOASSAYS FOR THE DETECTION OF AUTOANTIBODIES IN INFLAMMATORY IDIOPATHIC MYOPATHIES (IIM)

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Background

Myositis specific antibodies (MSA) represent not only important diagnostic tools, but also help to stratify patients into subsets with particular clinical features, treatment responses and disease outcome. These antibodies even have the potential to be used in classification criteria. Consequently, standardization of MSA is of high importance. Many laboratories rely on immunoprecipitation (IP) for the detection of MSA which however, will suffer regulatory challenges in the future. Therefore, reliable alternatives are mandatory. Recently, we identified significant variation between IP and line immunoassay (LIA) for the detection of MSA and myositis associated antibodies (MAA). In this study we aimed to compare the results from our previous study (1) to the results obtained with novel fully automated bead based assays for the detection of autoantibodies to MSA and MAA.

Method

A total of 66 sera from patients with idiopathic inflammatory myopathy (IIM) were tested using three methods: IP, LIA (Euroimmun, Germany) and novel bead based immunoassays (Inova Diagnostics, US, research use only). The analysis focused on antibodies to SRP, MDA5, NXP-2 and Mi-2.

Results

Significant variations were observed among all methods. Overall, the novel assays show slightly better correlation with IP, but the *kappa* agreement was strongly dependent on the antibody tested.

	SRP	NXP-2	MDA5	Mi-2
BIA vs. LIA	-0.10	0.62	0.47	0.47
BIA vs. IP	0.24	0.77	0.54	1.00
LIA vs. IP	-0.08	0.51	0.64	0.46

BIA=bead immunoassay; LIA=line immunoassay; IP= immunoprecipitation

Conclusion

Overall, the novel assays showed improved correlation to IP for 3 out of the 4 analytes. Larger studies are required to further analyze the correlation between immunoassays for the detection of MSA.

AUTO1-0963
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

THE ROLE OF THE NEW AUTO-ANTIBODIES IN DEFINING SPECIFIC PHENOTYPES IN PATIENTS WITH DERMATOMYOSITIS/POLYMYOSITIS

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Background

Dermatomyositis and polymyositis (PM/DM) are inflammatory myopathies characterized by muscular weakness and inflammation. Some patients also present with characteristic skin changes, interstitial lung disease (ILD) or cancer, among other symptoms. Myositis-specific and myositis-associated autoantibodies (autoAb) have been found in patients. In addition, new specific AutoAb have been included in the diagnostic panels. To asses the clinical value of the new PM/DM-specific AutoAb in defining clinical phenotypes in our patients diagnosed with PM/DM.

Method

All patients with a suspicion of PM/DM admitted to Hospital Puerta del Mar (Cadiz, Spain) for the last 18 months were tested for anti-TIF1-γ, anti-NXP2, anti-MDA5 and SAE-1 AutoAb (New DM/PM-autoAb) by using immunoblot (Euroimmun, Germany). Clinical features were recorded.

Results

New DM/PM-AutoAb were detected in 3 patients. Patient 1 had anti-TIF1-γ AutoAb and showed an exclusive cutaneous phenotype. Neither ILD nor cancers were found. Patient 2 had anti-MDA5 AutoAb and showed a skin rash with progressive ILD. Patient 3 had Anti-NXP2 AutoAb and presented with severe skin changes without ILD or cancer. Patients did not show evident muscular weakness, although muscle enzymes were elevated in patients 2 and 3.

Conclusion

In our patients, anti-MDA5 AutoAb was a good marker for ILD and NXP2 AutoAb indicated severe skin disease. Neither TIF1-γ nor NXP2 were markers for associated cancer in PM/DM. These results support the role of the new DM/PM-AutoAb in defining the clinical phenotype and the prognosis of DM/PM patients.

AUTO1-0521
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

ANTI-SIGNAL RECOGNITION PARTICLE MYOPATHY IN A PAEDIATRIC PATIENT: CASE REPORT OF CLINICAL AND LABORATORIAL FEATURES

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Background

Anti-Signal Recognition Particle (anti-SRP) are myositis-specific antibodies usually associated with a severe and rapidly progressive myopathy that poorly responds to conventional therapy. These antibodies are mostly detected in adult patients; their presence in paediatric onset is seldom described.

Method

In this essay we report a case of a 16-years-old female patient suspected to have a neuromuscular disorder, who tested positive for anti-SRP antibody.

Results

The patient presented to the emergency department after a two year period of insidious but progressive onset of disease. She experienced symmetrical dominant proximal muscular weakness in upper and lower extremities with facial and cervical involvement sparing only eyelid and ocular muscles, symptoms that hindered her daily activities. Upon examination generalized amyotrophy and hypoventilation were noted. No evidence of family history was found.

Laboratory data showed an elevation of muscle enzymes levels (creatine kinase of 6155 U/L, aspartate aminotransferase of 120 U/L, lactate dehydrogenase of 588 U/L) and serologic testing revealed the presence of high-titer fine dense speckled cytoplasmic staining (>1/1280) on HEp-2 cell substrate and anti-SRP antibodies. Muscular biopsy revealed signs of dystrophy; immunohistochemical study was normal.

At the time of submission of this abstract the patient was referenced to neuromuscular diseases consultation in a Portuguese central hospital.

Conclusion

The anti-SRP myopathy is rarely diagnosed entity in the paediatric population. The clinical and laboratorial findings supported the clinical suspicion contributing to the conclusive diagnosis for this patient.

AUTO1-0478
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

DISEASE PROGRESSION AND OXIDATIVE STRESS ARE ASSOCIATED WITH HIGHER SERUM FERRITIN LEVELS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background

Hyperferritinemia and oxidative stress have been implicated in the pathogenesis of multiple sclerosis (MS). The aim of the present study was to evaluate the serum levels of ferritin and to verify their association with oxidative stress markers and MS progression.

Method

This study included 164 MS patients, which were divided in two groups according to their levels of ferritin (cut off 125.6µg/L). Oxidative stress was evaluated by tert-butyl hydroperoxide-initiated chemiluminescence (CL-LOOH), advanced oxidation protein products (AOPP), carbonyl protein, nitric oxide metabolites (NO_x), sulfhydryl groups of protein and total radical-trapping antioxidant parameter (TRAP).

Results

MS patients with elevated levels of ferritin showed higher disease progression (p=0.030), AOPP (p=0.001), and lower plasma NO_x levels (p=0.031) and TRAP (p=0.006) than MS patients with lower ferritin levels. The multivariate binary logistic regression analysis showed that increased AOPP and progression of disease were significantly and positively associated with increase of ferritin. The combination of serum ferritin levels and oxidative stress markers were responsible for 13,9% in the disease progression.

Conclusion

In conclusion, our results suggest that ferritin could aggravate oxidative stress in patients with MS and contribute to progression of disease.

AUTO1-0515
POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

INSULIN RESISTANCE, ATHEROGENICITY, AND IRON METABOLISM IN MULTIPLE SCLEROSIS WITH AND WITHOUT DEPRESSION: ASSOCIATIONS WITH INFLAMMATORY AND OXIDATIVE STRESS BIOMARKERS AND URIC ACID

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Background

Depression is accompanied by metabolic disorders in iron metabolism, lipoproteins, and insulin resistance. We measured plasma levels of ferritin, iron, lipids, insulin, and glucose and computed the homeostasis model assessment (HOMA2IR) and atherogenic index of plasma (AIP) in MS patients with and without depression and healthy controls.

Method

Explanatory variables were serum uric acid, interleukin (IL)-6, lipid hydroperoxides (CL-LOOH), albumin, and C-reactive protein (CRP). Depression was assessed using the Hospital Anxiety and Depression Scale (HADS), neurological disability using the Expanded Disability Status Scale (EDSS), and disease progression using ΔEDSS over five years earlier.

Results

HOMA2IR and insulin were predicted by diagnosis (increased in MS), age and body mass index (BMI); AIP by diagnosis, sex, BMI, CRP, and uric acid; triglycerides by

diagnosis (higher in MS without depression), age, BMI and uric acid; ferritin by diagnosis (higher in MS), sex, CRP, and albumin; and iron by albumin. The HADS score was significantly predicted by ΔEDSS, gastro-intestinal symptoms, iron (inverse), and age.

Conclusion

MS is characterized by significantly increased insulin resistance, which is determined by increased insulin levels; and increased ferritin, a biomarker of inflammation. Depression in MS is not associated with increased insulin resistance and atherogenicity but with lowered iron

AUTO1-0444
PRECISION (PERSONALIZED) MEDICINE IN AUTOIMMUNITY

AUTOANTIBODY PROFILING USING HIGH-DENSITY PROTEIN MICROARRAYS

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Background

With infrastructure and know-how on high-throughput protein array technologies, the Autoimmunity Profiling facility at SciLifeLab KTH Stockholm (www.scilifelab.se/facilities/autoimmunity-profiling) offers comprehensive screening of autoantibody repertoires in various human body fluids.

Method

Proteome wide or custom designed protein and peptide arrays are available for autoantibody reactivity profiling or antibody specificity analysis. The facility has generated the world's largest protein array, with 42,000 unique protein fragments produced within the Human Protein Atlas project, representing 94% of the protein coding genes, which is used in untargeted exploratory screening. The resource of protein fragments is used to create tailored arrays on a bead array format that allows for the parallel analysis of 384 antigens in 384 patient samples. In addition, peptide arrays can also be generated for epitope mapping purposes. Instrumentation and know-how is available for generating customized spotted protein microarrays as well as read-out and image analysis of commercially available protein microarrays.

Results

Conclusion

AUTO1-0453
PRECISION (PERSONALIZED) MEDICINE IN AUTOIMMUNITY

PRESENCE OF ANTI-INFLIXIMAB AS A PREDICTIVE FACTOR FOR INFLIXIMAB TREATMENT FAILURE

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Background

Therapeutic drug monitoring of infliximab (IFX) and anti-infliximab (anti-IFX) antibodies is crucial to evaluating patients on a personalized level in Rheumatology and Gastroenterology.

The aims of the study were to:

-determine, whether anti-IFX levels are detected with *in-house* competitive ELISA (cELISA) and Reporter Gene Assay (RGA), in samples which were negative in bridging ELISA (bELISA) and

-predict maintenance of IFX therapy or treatment failure.

Method

Samples were sent from Departments of Rheumatology and Gastroenterology, University Medical Center Ljubljana, for routine IFX analysis. Samples tested as negative in IFX ELISA (Table 1) were analysed in apDia bELISA and later in cELISA and RGA. Clinical data were collected from medical records.

Table 1: Patients' characteristics

Characteristics	Samples (n=56)
Sex	
Female, n (%)	33 (59%)
Male, n (%)	23 (41%)
Disease	
Inflammatory bowel diseases, n (%)	23 (41%)
Chronic rheumatic diseases, n (%)	33 (59%)
Mean age at sampling time, years (range)	49 (19-86)
Mean time of IFX therapy, years (range)	2.9 (0.1-15)
Concomitant immunosuppressives, n (%)	
Methotrexate	14 (25%)
Methylprednisolone	9 (16%)
Leflunomide	5 (9%)
Azathioprine	4 (7%)
No therapy	24 (43%)

Results

Samples from 56 patients were collected and 24/56 (43%) samples were negative for anti-IFX in bELISA and their therapies were optimized by the clinicians. 6/24 (25%) above-mentioned samples were positive in cELISA and RGA. The therapy was switched for 3 patients (50%), while the other 3 (50%) remained on therapy at observation time. In the group of 18 (75%) patients negative in bELISA, cELISA and RGA, 12 (67%) patients remained on therapy, while 6 (33%) patients developed drug failure.

Conclusion

Our preliminary data, in a small group of patients, showed that positive results in cELISA or RGA in samples with negative bELISA, can predict treatment failure in 50% of the cases, while a negative result in 67% negative samples in bELISA may predict that patients will remain on IFX therapy, meaning that anti-IFX antibodies were not the reason for undetectable IFX.

AUTO1-0733
PREDICTION, MONITORING AND PREVENTION

RELATIONSHIP OF BIOMARKERS, ULTRASOUND (US) SIGNS OF JOINT DAMAGE AND RADIOGRAPHIC PROGRESSION IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

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Background

Objective: to identify the relationship between cytokines, US signs and radiologic progression in RA patients.

Method

35 patients with early RA use MTX and/or biologic therapy in accordance with the treat-to-target concept. Serum cytokine concentrations were determined using the xMAP multiplexing technology baseline, 3 and 6 months after the start of therapy. We analyzed absolutely levels and theirs changes(Δ).US with power Doppler (PD) were performed baseline, 3, 6, 9 and 12 months after the start of therapy. X-ray examination was conducted baseline and at 12 month of therapy with an assessment of X-ray changes by Sharp-van der Heijde scores.

Results

IL1β, L6, IL12, IL15, TNFα levels decreased by 3month. Significant differences in PD-persistent group at the end of observation were revealed only for IL6 and TNFα, and with X-ray progression for Δ IL17 at 6-month. At baseline a positive correlation was found between PD and IL1β (r=0.34), IL6 (r=0.42). In the PD-group concentration of IL6 baseline was significantly higher: 75.2 (37.9, 101.7) vs 38.7 (19.2, 59.6); by 6-month level of TNFα in this group also higher: 67.6 (34.3, 125.5) vs 38.8 (21.9; 67.2). Radiographic progression was detected in 6 (17%) patients with significantly higher PD. ΔIL17 and ΔFGF at 3month and ΔIL17 at 6month correlated significantly with the sum of erosions by X-ray (r=0.43, r=0.37, r=0.38, respectively).

Conclusion

The revealed relationship of PD-US, X-ray progression and biomarkers of inflammation in RA confirm the role of ultrasound as a method of independent evaluation of the course and outcomes of the disease.

AUTO1-1036
PREDICTION, MONITORING AND PREVENTION

DETECTION OF ANTI-DRUG ANTIBODIES IN PATIENTS WITH ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS TREATED WITH TNF INHIBITORS

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Background

The presence of anti-drug antibodies in inflammatory diseases is often accompanied by lack of response to treatment, and subsequently influences medical decision-making in these cases. The aim of our study was to assess circulating TNF inhibitor values as well as anti-drug antibodies in patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA) treated with adalimumab, etanercept and infliximab.

Method We included 36 patients with AS and 22 patients with RA treated with TNFα inhibitors. Serum levels of adalimumab, etanercept and infliximab as well as anti-drug antibodies were assessed through enzyme-linked immunoassay (ELISA). Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were analyzed in all participants. We evaluated disease activity using DAS28-CRP in RA and ASDAS-CRP as well as BASDAI in AS.

Results Serum drug levels were significantly higher in patients with AS treated with adalimumab compared to RA ($p=0.025$). Decreased serum drug levels as well as high anti-drug antibody values correlated with disease activity, ESR and CRP in patients treated with adalimumab and infliximab in both groups ($p<0.05$). This relationship was not identified in participants treated with etanercept. The latter was found to associate with normal circulating drug levels as well as decreased antibody values. All RA patients treated with infliximab exhibited subnormal circulating TNF inhibitor levels and tested positive for anti-drug antibodies.

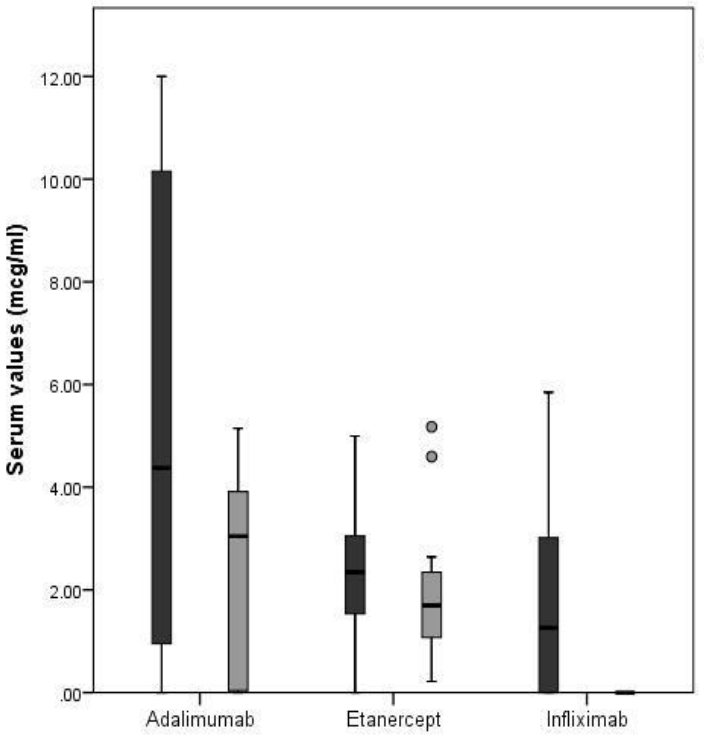

Figure 1. Circulating TNF inhibitor values in patients with AS and RA

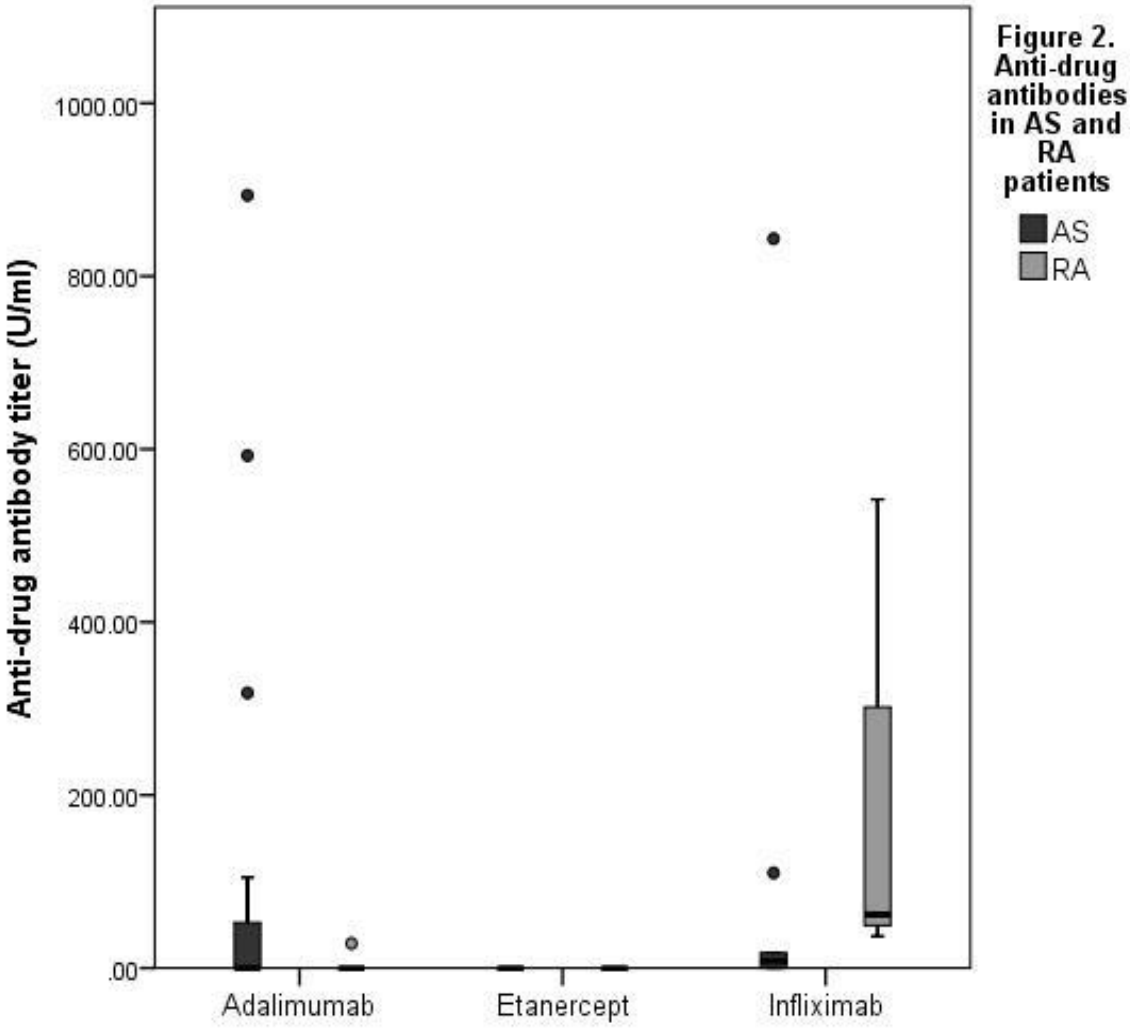

Figure 2. Anti-drug antibodies in AS and RA patients

Conclusion

Our study supports the relationship between anti-drug antibodies and high disease activity in RA and AS patients treated with infliximab and adalimumab. We found no association with anti-etanercept antibodies given their known non-neutralizing nature.

AUTO1-0699
PREDICTION, MONITORING AND PREVENTION

FUNCTIONAL CAPACITY MEASURED BY HAQ IN PATIENTS WITH RHEUMATIC DISEASES FROM A COLOMBIAN POPULATION: AN OPEN POPULATION STUDY

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Background

Functional capacity is an important indicator of quality of life that is affected in different pathologies and is susceptible to intervention in early stages once it is recognized. In rheumatic diseases, functional limitation has a great impact that is evidenced by multiple degrees of long-term disability.

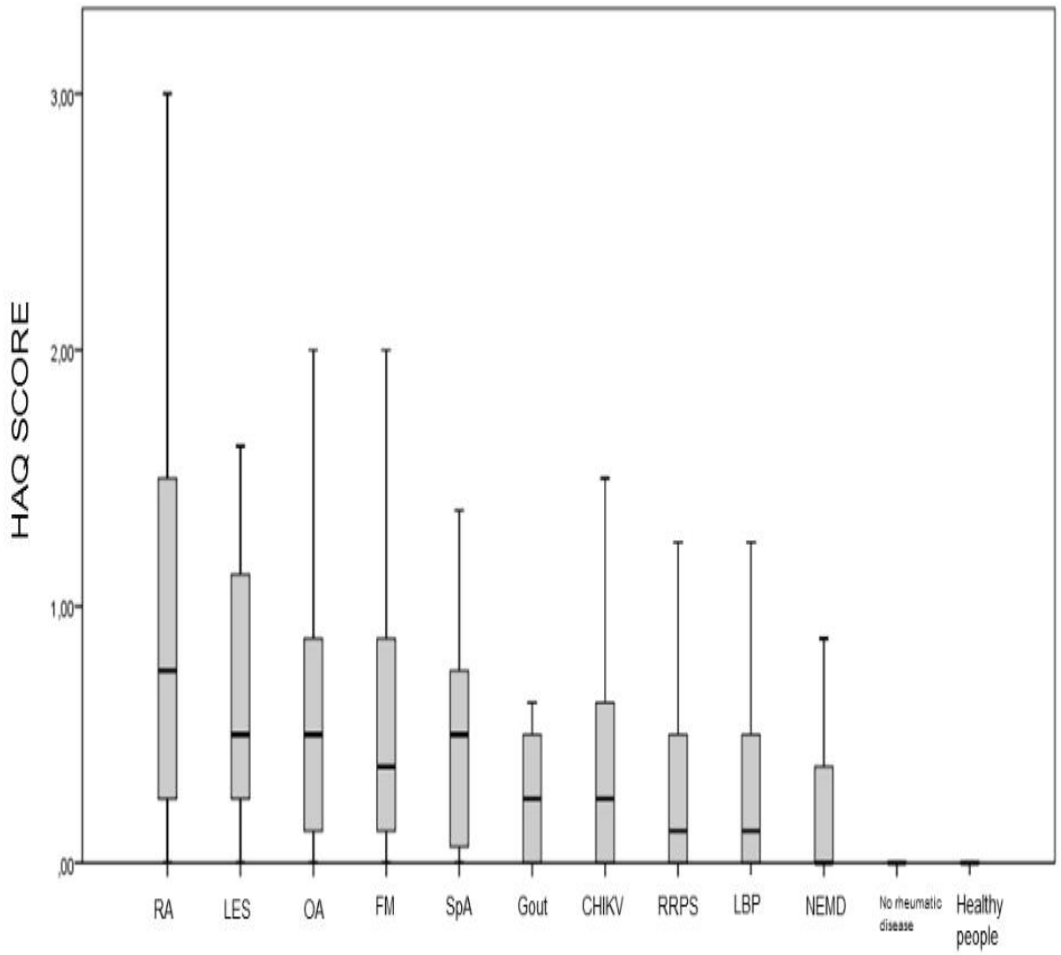
Method

Within a prevalence study of rheumatic disease in Colombia, the measure of functional capacity was self-reported by 2274 patients with rheumatic diseases, 1104 disease-free patients and 642 patients with non-rheumatic diseases. The HAQ instrument (Health Assessment Questionnaire) was used, where major functional limitation is scored 3 and not limitation 0.

Results

Patients with rheumatic diseases reported a higher degree of functional limitation compared to disease-free persons and non-rheumatic patients ($p< 0,001$). The score obtained in patients with RA was 0,88 ± 0,72 compared to 0,06 ± 0,22 and 0,01 ± 0,14 of the population with non-rheumatic diseases and disease-free people respectively. The HAQ score in the remaining diseases was 0,67 (SD± 0,62) for SLE, 0,59 (SD± 0,58) for OA, 0,56 (SD± 0,57) for FM and0,52 (SD± 0,43) for SpA. **Figure 1**.

Figure 1. Functional capacity of patients with rheumatic diseases, with non-rheumatic diseases and disease-free population



**RA: Rheumatoid arthritis; SpA: Spondyloarthritis; SLE: Systemic Lupus Erythematosus; OA: Osteoarthritis; FM: Fibromyalgia; RRPS: Rheumatic Regional Pain Syndromes (Rotator cuff tendinopathy, shoulder bicipital tendinopathy, lateral and medial medial epicondylalgia, Quervain's tendinopathy, carpal tunnel syndrome, Dupuytren's contracture, trochanteric syndrome, anserine bursitis, achilles tendonopathy, plantar talalgia); NEMD: non-specific musculoskeletal disease; LBP: Low Back Pain.

** Non-rheumatic diseases: hypertension, diabetes, cardiopathy, cancer, TB, mental disorders, Obesity, Venous Insufficiency of lower limbs, Stroke, Epilepsy, Migraine

Conclusion

Patients with rheumatic diseases have a lower functional capacity compared to a healthy population and non-rheumatic patients. Patients with RA had a higher degree of disability followed by patients with SLE and OA.

AUTO1-0717
PREDICTION, MONITORING AND PREVENTION

QUALITY OF LIFE IN PATIENTS WITH RHEUMATIC DISEASES, NON-RHEUMATIC DISEASE AND HEALTHY POPULATION: AN OPEN POPULATION STUDY

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Background

The measurement of quality of life is fundamental to estimate the health status in the general population. It is used as an indicator of public health. The EQ-5D-3L is one of the most used instruments worldwide.

Method

The EQ-5D-3L survey was implemented in 6,693 people. An analytical study was developed to estimate the health state in 6 Colombian cities.

Results

The main non-rheumatic diseases found were cardiovascular diseases and mental disorders. Regarding the EQ-5D-3L dimensions, 20% (n=53) of patients with these diseases reported moderate involvement of pain and physical discomfort, as well as anxiety and depression. Twenty percent of patients with cerebrovascular disease reported moderate limitation for mobility and 10% (n=11) of patients with epilepsy had a severe involvement in mobility dimension. Patients with cardiovascular diseases reported moderate difficulties in carrying out daily activities. **Table 1.**

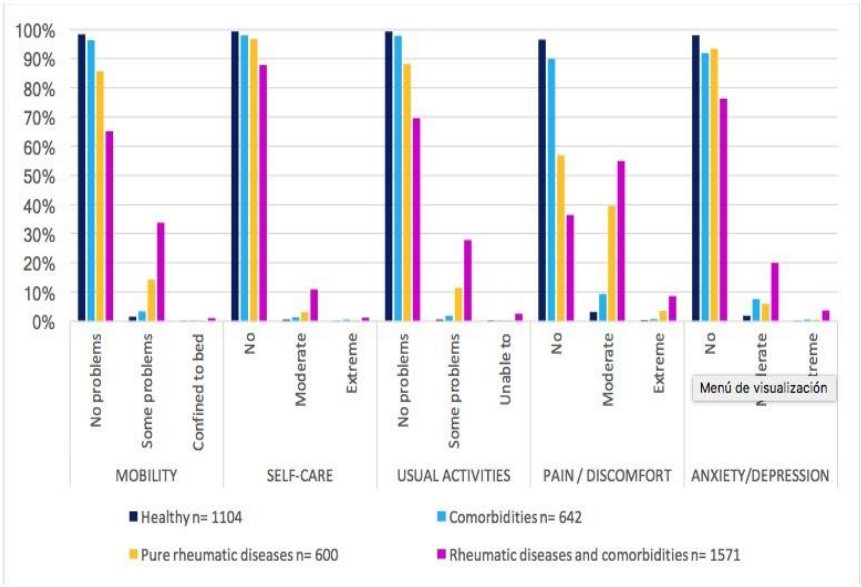
Table 1. Dimensions of EQ-5D-3L in patients with non-rheumatic diseases

		HBP n= 201	Venous insufficiency n= 190	Migraine n= 158	Mental diseases n= 137	Obesity n= 95	Diabetes n= 55	CVD n= 53	Cancer n= 13	Stroke n= 11	Epilepsy n= 11	TB n= 7
MOBILITY	No problems	93,5	95,8	98,1	97,1	93,7	96,4	90,6	100	81,8	90,9	100
	Some problems	6,5	4,2	1,9	2,9	6,3	3,6	9,4	0	18,2	0	0
	Confined to bed	0	0	0	0	0	0	0	0	0	9,1	0
SELF-CARE	No	97,5	97,9	98,7	100	98,9	98,2	94,3	100	90,9	90,9	100
	Moderate	2	2,1	0,6	0	1,1	1,8	3,8	0	9,1	0	0
	Extreme	0,5	0	0,6	0	0	0	1,9	0	0	9,1	0
USUAL ACTIVITIES	No problems	95,5	97,4	99,4	99,3	97,9	100	92,5	100	90,9	90,9	100
	Some problems	4	2,6	0,6	0,7	2,1	0	7,5	0	9,1	0	0
	Unable to	0,5	0	0	0	0	0	0	0	0	9,1	0
PAIN / DISCOMFORT	No	87,1	89,5	86,1	84,7	88,4	92,7	84,9	92,3	81,8	100	100
	Moderate	11,9	9,5	12	14,6	11,6	5,5	13,2	7,7	18,2	0	0
	Extreme	1	1,1	1,9	0,7	0	1,8	1,9	0	0	0	0
ANXIETY/ DEPRESSION	No	91	93,7	92,4	76,6	94,7	96,4	84,9	92,3	90,9	81,8	100
	Moderate	8,5	6,3	7,6	22,6	5,3	1,8	15,1	7,7	9,1	18,2	0
	Extreme	0,5	0	0	0,7	0	1,8	0	0	0	0	0

* The values of each of the dimensions of the instrument are expressed in %
** HBP: high blood pressure, CVD: cardiovascular disease, TB: tuberculosis
*** Mental disorders: anxiety, nervousness or depression.

In the disease-free population and patients with non-rheumatic diseases, the reported quality of life had a very similar behaviour. Patients with rheumatic diseases and comorbidities had greater involvement in quality of life predominately in pain and physical discomfort (more than 50% of the patients). **Figure 1.**

Figure 1. EQ5D-3L in patients with non-rheumatic diseases, rheumatic diseases and healthy patients



* Pure rheumatic diseases: RA: Rheumatoid arthritis; SpA: Spondyloarthritis; SLE: Systemic Lupus Erythematosus; OA: Osteoarthritis; FM: Fibromyalgia; RRPS: Rheumatic Regional Pain Syndromes (Rotator cuff tendinopathy, shoulder bicipital tendinopathy, lateral and medial medial epicondylalgia, Quervain's tendinopathy, carpal tunnel syndrome, Dupuytren's contracture, trochanteric syndrome, anserine bursitis, achilles tendonopathy, plantar talalgia); NEMD: non-specific musculoskeletal disease
** Comorbidities: HBP, DM, Cardiopathy, Cancer, TBC, Psychiatric, Obesity, MMII Venous Insufficiency, Stroke, Epilepsy, Migraine

Conclusion

Patients with rheumatic diseases had a lower quality of life compared to the general population; and it is even worse in patients with rheumatic diseases and comorbidities, mainly due to involvement in mobility, daily activities, and increased pain and discomfort. We recognized specific factors of intervention in the comprehensive health care. The general interest is to improve the quality of life and reduces long-term disability of patients with rheumatic diseases.

AUTO1-0718
PREDICTION, MONITORING AND PREVENTION

QUALITY OF LIFE IN COLOMBIAN RHEUMATIC PATIENTS MEASURED BY EQ-5D-3L

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Background

Rheumatic diseases are an important cause of chronic pain, disability and deterioration of quality of life. In Colombia, this last aspect has not been evaluated in an open population.

Method

Within the development of a prevalence study of rheumatic diseases in Colombia under the COPCORD strategy, quality of life was evaluated using the EQ-5D-3L instrument. Inhabitants from six cities (Bogotá, Medellín, Cali, Barranquilla, Bucaramanga and Cúcuta) answered the questionnaire.

Results

From a total of 4020 evaluated individuals, 2274 had rheumatic disease, 642 had a non-rheumatic disease, and 1104 were free-disease individuals.

Only a quarter of patients with Spondylarthritis (SpA) and Rheumatoid arthritis (RA) (25% (n=32) and 26% (n=68) respectively) showed no pain when compared to almost the total of free-disease population and patients with non-rheumatic disease. More than 50% of patients with RA and SpA had problems in the mobility dimension. Around 50% of patients with RA and Systemic lupus erythematosus (SLE) (n=6) were affected for performing daily activities. In terms of anxiety and depression, the most affected were patients were those with Fibromyalgia (FM), RA, and SLE. Patients with RA and FM had moderate difficulties in personal care dimension. **Table 1.**

Table 1. Quality of life measured by EQ-5D-3L in rheumatic patients, non-rheumatic and healthy patients. Study in open population.

		AR n= 68	SpA n= 32	LES n= 6	OA n= 747	Gout n= 19	FM n= 34	RRPS n= 357	CHIKV n= 178	Back pain n= 249	NEMD n= 584	No rheumatic diseases n= 642	Healthy people n= 1104
PAIN / DISCOMFORT	No	26,0	25,0	50,0	34,3	47,4	26,5	39,8	47,2	43,0	55,3	89,9	**96,5**
	Moderate	69,1	59,4	33,3	55,4	47,4	58,8	53,2	44,4	52,2	41,3	9,3	**3,2**
	Extreme	10,3	15,6	16,7	10,3	5,3	14,7	7,0	8,4	4,8	3,4	0,8	**0,4**
MOBILITY	No problems	44,1	46,9	50,0	60,5	63,2	67,6	73,3	76,4	76,7	82,5	96,4	**98,4**
	Some problems	54,4	53,1	50,0	38,0	36,8	32,4	26,1	22,5	23,3	16,4	3,4	**1,5**
	Confined to bed	1,5	0,0	0,0	1,5	0,0	0,0	0,3	1,1	0,0	1,0	0,2	**0,1**
USUAL ACTIVITIES	No problems	47,1	56,3	50,0	68,9	63,2	52,9	76,2	82,6	76,7	85,1	97,8	**99,4**
	Some problems	48,5	43,8	50,0	27,7	36,8	47,1	23,2	16,9	22,9	13,4	1,9	**0,5**
	Unable to	4,4	0,0	0,0	3,3	0,0	0,0	0,6	0,6	0,4	1,5	0,3	**0,2**
ANXIETY/DEPRESSION	No	66,2	71,9	66,7	78,4	78,9	67,6	82,1	89,3	82,3	85,3	91,9	**98,0**
	Moderate	30,9	25,0	16,7	17,4	21,1	26,5	16,2	9,6	15,7	12,5	7,6	**1,9**
	Extreme	2,9	3,1	16,7	4,1	0,0	5,9	1,7	1,1	2,0	2,2	0,5	**0,1**
SELF-CARE	No	70,6	81,3	100,0	88,8	84,2	76,5	91,3	94,0	93,2	93,7	98,1	**99,4**
	Moderate	27,9	18,8	0,0	9,5	10,5	23,5	8,1	5,9	6,8	5,8	1,4	**0,5**
	Extreme	1,5	0,0	0,0	1,7	5,3	0,0	0,6	0,6	0,0	0,5	0,5	**0,1**

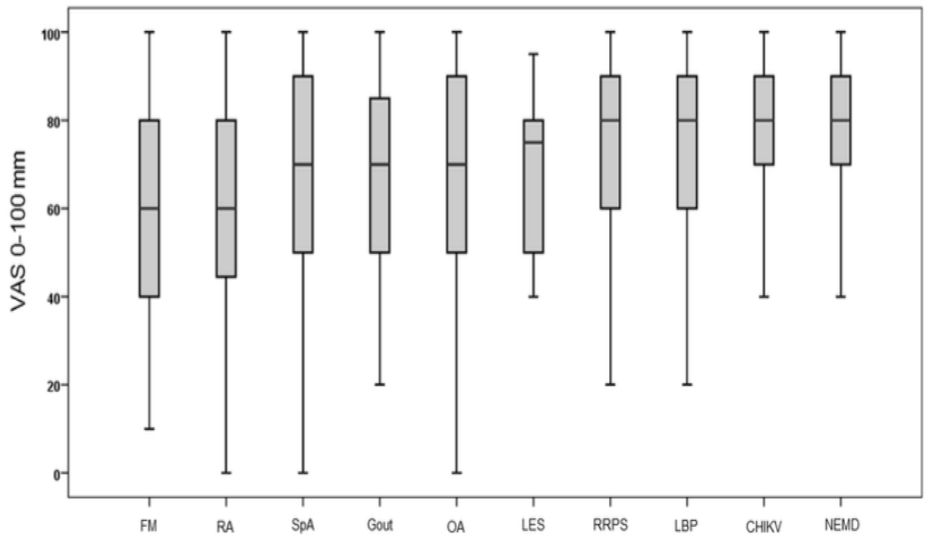
* The values of each of the dimensions of the instrument are expressed in %.

** COPCORD: Community Oriented Program for Control of Rheumatic Diseases.

*** AR: Rheumatoid arthritis; SpA: Spondyloarthritis; SLE: Systemic Lupus Erythematosus; OA: Osteoarthritis; FM: Fibromyalgia; RRPS: Rheumatic Regional Pain Syndromes (Rotator cuff tendinopathy, shoulder bicipital tendinopathy, lateral and medial epicondylalgia, Quervain's tendinopathy, carpal tunnel syndrome, Dupuytren's contracture, trochanteric syndrome, anserine bursitis, achilles tendonopathy, plantar talalgia); NEMD: non-specific musculoskeletal disease; Non-rheumatic diseases: HBP, DM, Cardiopathy, Cancer, TBC, Psychiatry, Obesity, MMII venous insufficiency, stroke, epilepsy, migraine.

The results of the visual analogue scale (VAS) of quality of life are shown in **figure 1**.

Figure 1. Quality of life in rheumatic patients in Colombia EQ-5D-3L VAS: 0 -100mm



FM: fibromyalgia, RA: rheumatoid arthritis, SpA: spondyloarthritis, OA: osteoarthrosis, SLE: generalized lupus erythematosus, RRPS: Rheumatic Regional Pain Syndromes, CHIKV: Chikungunya fever, NEMD: non-specific musculoskeletal disease.

Conclusion

Patients with RA had the most decrease in all dimensions of the EQ-5D-3L, followed by patients with SpA and SLE. In patients with OA, pain and discomfort were frequent affecting dimensions in mobility and daily activities. Patients with FM had the worst VAS measures.

AUTO1-0315
PREDICTION, MONITORING AND PREVENTION

CARDIOVASCULAR RISK IN BEHCET'S DISEASE – THREE YEARS OF FOLLOW UP

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Background

Behcet's Vasculitis(BD)is an immune-mediated, multisystemic chronic inflammatory disease.Systemic inflamation contributes towards vascular aging and thus increased cardiovascular risk(CR).Arterial stiffness measured by pulse wave velocity(PWV)is an accurate measure for vascular aging. The objective of this study is to assess whether PWV analysis is correlated with premature aging and increased global CR in patients with BD in comparison to general population controls.

Method

Observational study was designed. 30patients followed at Autoimmune Diseases clinic were included. Exclusion criteria were: overlap with other immune mediated disease, not coping with treatment and abandonment of the clinical appointments. Other cardiovascular morbidities were considered Informed consent was taken. Measurement of peripheral and central blood pressure, anthropometric parameters (weight, height),PWV was performed in two separate visits 2014 and 2017.Statistical comparison with general population controls paired by age and gender.

Results

Three patients were excluded, one-abandonment; two-due to the appearance of another autoimmune disease. Of the 27patients included, 61.5%female;38.4%male, with an average age in2017 of48.3years. The average PWV in 2014was 6.56m/s against 8.95m/s found in 2017.Wilcoxon test was performed, with statistical significance of the increase in PWV compared to general population in 2014and 2017 ($p<0.01$). However, there was no significant difference in CR between BD and general population in 2014but in2017 a direct correlation between PWV and increased CR was obtained.

Conclusion

Although in 2014no direct connection was found between BD and increased vascular aging,2017results confirmed that patients had a statistically significant increase in PWV and CR.However the authors believe that it would be premature and further follow up studies are needed.

AUTO1-0580
PREDICTION, MONITORING AND PREVENTION

CARDIOVASCULAR RISK EVALUATION OF BEHCET'S PATIENTS, FOLLOWED IN SENHORA DA OLIVEIRA HOSPITAL, IN 2017

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Background

Behcet's disease (BD) is a chronic inflammatory syndrome with mucocutaneous and systemic manifestations. Systemic vasculitis, involving arteries and veins, contribute to vascular aging, with an increase in arterial stiffness that can be inferred from the Pulse Wave Velocity (PWV) measurement. Intima media thickness (IMT) evaluation also allows vascular alterations detection. These alterations increase cardiovascular risk.

Method

49 patients were included. Anthropometric, sociodemographic, laboratorial, comorbidities, medication, peripheral and central blood pressure, Systematic Coronary Risk Evaluation, PWV and common carotid artery IMT data were evaluated. A linear regression model was performed to evaluate the impact of the variables on the PWV. After exclusion of patients with major identifiable cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus and obesity) a subgroup of 26 patients was created and values compared.

Results

PWV median value was 8.4 m/s, 30.6% PWV>90th percentile (pc90) of the normal population and 16.3% with target organ lesion. IMT abnormal values and plaques were observed in 10.4% and 41,7%, respectively. In regression model, systolic blood pressure and IMT contribute to PWV, with R^2=31,8%. In the subgroup, 46.2% presented PWV>pc90 and 19.2% target organ lesion. 1 patient presented abnormal IMT and 5 presented plaques.

Conclusion

Integrated analysis of cardiovascular risk factors allowed early abnormalities detection and the adoption of strategies to change the disease's course. In the subgroup, PWV>pc90 and target organ lesion were recorded in greater proportion than the total group. Inflammation's role may justify the values found, but should be clarified.

AUTO1-0641
PREDICTION, MONITORING AND PREVENTION

ROLE OF ANTI-CCP , HSCRP AND MUSCULOSKELETAL ULTRASOUND IN DETECTION OF DISEASE ACTIVITY AND SEVERITY OF JUVENILE IDIOPATHIC ARTHRITIS

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Background

Juvenile idiopathic arthritis is a common systemic autoimmune inflammatory disease. Anti-CCP is important biomarker to differentiate those patients with aggressive JIA. hs CRP could identify patients in clinical remission and their risk of disease relapse. Ultrasound on the joints is more sensitive in the detection of disease activity than clinical examination alone. The aim: evaluate the role of anti-CCP 2and hs CRP, MSUS in early detection of activity of JIA.

Method

Assessment of the disease activity of JIA using JADAS27. MSUS in two planes (longitudinal and transverse), RF, hsCRP and Anti-CCP were done.

Results

60 JIA patients; (41.66%) males and (58.33%) females. Their mean age was 7.9. Their mean disease duration 3.5. They were divided according to disease activity into 2 groups: group 1: 30 patients with JADAS27 score <3.8, group 2: 30 JIA patients of high disease activity according to JADAS27 score ≥3.8 There was highly significant positive correlation between ESR, CRP, hs CRP and JADAS27. On other hand, there was non-significant positive correlation between anti CCP levels and JADAS27. Global ultrasound score had highly significant positive correlation with JADAS27 $P < 0.001$. Global ultrasound score had significant positive correlation with hs CRP. Diagnostic performance of different parameters in discrimination of disease activity of group I and group II ROC curve, hs CRP was more sensitive in early detection of disease activity followed by ultrasound score while anti CCP and routine CRP showed lower global sensitivity

Conclusion

hs CRP, MSUS Doppler are important tools in detection of activity of JIA children.

AUTO1-0766
PREDICTION, MONITORING AND PREVENTION

Definition of a new biomarker of disease activity in Rheumatoid Arthritis

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Background

In the inflammatory events of rheumatoid artrhitis (RA), a policlonal excess of free light chains kappa (K) and lambda (L) is produced. The sum of serum levels of K and L, defined as "(K+L) Index", could be associated with inflammatory activity. The aims of the study are 1)compare (K+L) index between donors and RA patients, 2)Evaluate the diagnostic accuracy of (K+L) index in active disease, 3)Correlate (K+L) index with parameters of RA.

Method

Study based on 69 donors and 73 patients with RA (28 remission:45 active disease). Disease activity evaluated using DAS28 score. Pairwise comparison was carried out with Mann-Whitney test, ROC curve was used to evaluate the efficacy of (K+L) index and Spearman correlation analysis was used for assessing the relationship between quantitative variables.

Results

Objective-1:(K+L) index was higher in RA patients than healthy controls: 37.86 mg/L vs. 24.99 mg/L ($p<0.0001$). Between RA patients;
(K+L) index in patients with active RA was significantly higher than those of patients in remission: 38.29 mg/L vs. 33.73 mg/L ($p=0.018$).

Objective-2: The AUC in patients with active RA was 0.855 for (K+L) index. The optimal cut-off determined by ROC curve for (K+L) index was 32.98 mg/L.

Objective-3:A good linear correlation was found between (K+L) index and DAS28 score ($r=0.503$; $p<0.0001$) and VSG ($r=0.270$; $p=0.02$).No significantly correlation was found with PCR, FR and ACPA.

Conclusion

Levels of serum “(K+L) index” in patients with active RA were higher than those of patients in remission and of donors. An optimal cut-off of 32.98 mg/L allows us to diagnose activity states.

AUTO1-0655
PREDICTION, MONITORING AND PREVENTION

REACTION OF ERYTHROPHAGOCYTOSIS AS AN IMMUNOLOGICAL TEST FOR EARLY DIAGNOSTICS OF CORONARY HEART DISEASE IN WOMEN

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Background

Autoimmune damage to the endothelium is still of interest to scientists. In patients having CHD circulating immune complexes containing cholesterol and other antigens that are fixed to the endothelium and cause damage.

Objective: To study the reaction erythrophagocytosis (EF) as an immunological test for the early diagnosis of CHD in women.

Method

Reaction of EF was studied in 46 women with CHD (23 in each group), aged 20-59 years, who were in inpatient and outpatient care. 21 women were of fertile age, and 25 - in the menopause period. The control group of the study was 10 practically healthy women of similar age. All we surveyed investigated lipid profile and reaction EF.

Results

EF level in 10 healthy subjects was on average 0,8%±0,3% if it is 8 per 1000 leukocytes neutrophils. Morphological picture of EF most often observed in patients with CHD in II group - an average of 12.9%, i.e., 129 leukocytes by 1000 neutrophils, indicating an expressed autoimmune reaction in these patients. EF more detected in menopausal women 13.2±1.3%, as compared with patients fertile age 10,7%±1,3%. Thus, in patients with CHD revealed an increase EF almost 10 times as compared with the control group that allows using the morphological picture of FE as a laboratory test to detect autoimmune component in patients with CHD, both in acute and chronic forms.

Conclusion

10-fold increase in the % EF in women with CHD as compared to healthy individuals, can allow using it as an immunological test for the early diagnosis of CHD in women.

AUTO1-0993
PREDICTION, MONITORING AND PREVENTION

ADHERENCE AND COMPLIANCE TO THE BIOLOGIC TREATMENT IN PATIENTS WITH RHEUMATIC DISEASES

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Background

In the last decades, with the invention of the biologic agents, a new era in the treatment of the inflammatory joint diseases occured . The aim of this study was to calculate the adherence and compliance to the treatment with Tumor necrosis factor- alpha (TNF-α) blockers (adalimumab) in patients with different rheumatologic diseases over a period of 5 years.

Method

We studied 156 patients with inflammatory joint diseases - 66 with RA, 48 with AS and 42 with PsA. We analyzed the activity of the disease, age of the patients, number of hospitalizations, education and concomitant treatment. Patients were followed-up every 6 months and during their outpatient visits they completed questionnarries containing all the required information. Data was tested using SPSS v.24.

Results

During the first 6 months only 2 patients (1,28%) discontinued treatment with the TNF-α blocker due to pulmonary bacterial infection. Over the next visits a gradual decrease in the number of the patients, treated with TNF-α inhibitors, was observed. At the end of the fifth year only 54,21 % of the patients were still on their initial therapy. We found out that the adherence of the patients to the therapy depended on the disease activity, age of the patients, number of hospitalizations, education and the number of the concomitant medications ($p<0.05$).

Conclusion

The compliance and adherence of the patients to the treatment with TNF-α blockers depend on social and economic factors of the patient, healthcare system, level of education and the behavior of the rheumatologists.

AUTO1-0994
PREDICTION, MONITORING AND PREVENTION

INFLUENCE OF ALCOHOL CONSUMPTION OVER THE PRODUCTION OF ANTI-DRUG ANTIBODIES AGANST THE BIOLOGIC AGENTS

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Background

Through the years a variety of factors, influencing the production of anti-drug antibodies (ADA) in patients with inflammatory joint diseases, treated with biologic agents, were studied. The aim of this study was to prove the correlation between the production of the ADA and the alcohol intake in patients treated with Tumor necrosis factor- alpha (TNF-α) blockers.

Method

We analyzed 93 patients with RA, PsA, AS, who were tested with ELISA method, kits "IDK® TNFα ELISA", manifactured by Immundiagnostik, were used, for presence of ADA on 0, 6, 12, 24 month of their treatment with adalimumab (Humira). After informed consent was obtained all the patients completed questionnarries regarding the alcohol intake, type of alcohol used and its quantity. All the results were analyzed with SPSS software v.24 , significance p <0,05.

Results

Out of 93 patients 4 (4,30%) declared systemic use of 100 ml concentrated alcohol ,5 patients admited 100 ml concentrated alcohol intake three times a week. None of the patients declared usage of more than 100 ml alcohol daily and none declared beer abuse. Patients with systemic use of alcohol had more frequent production of ADA during their treatment on 6, 12, 24 month ($p<0.05$). Clinical findings, laboratory tests and the disease activity indexes were worsened significantly in patients that have previously declared alcohol usage of 50-100ml daily ($p<0.05$).

Conclusion

Patients using even small doses of alochol (100 ml daily concentrated alcohol) have more frequent incidence of antibodies against TNF- α inhibitors which leads to negative impact on treatment.

AUTO1-0995
PREDICTION, MONITORING AND PREVENTION

CORRELATION BETWEEN THE PRESENCE OF ANTI-DRUG ANTIBODES AND THE DISEASE SEVERITY IN PATIENTS WITH INFLAMMATORY JOINT DISEASES

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Background

Inflammatory joint diseases such as Ankylosing Spondylitis (AS), Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) are now subject to interest for the rheumatologists due to the complicated citokine network and the successful treatment with biologic agents. Aim of this study was to prove the influence of the anti-drug antibodies on the disease activity in patients treated with TNF-alpha inhibitor (adalimumab), evaluated with indexes for disease activity-DAS28, BASDAI, DAPSA.

Method

We analyzed 93 patients with AS, RA, PsA -mean age 49±7 years, 55-women and 38-men. All were treated with adalimumab. Patients were tested for presence of ADA on 0,6,12,24 month of the initiation of treatment through ELISA method- kits “IDK® TNFα “ manufactured by Immundiagnostik. Patients were divided in two groups-A-without antibodies and B-with ADA against adalimumab. For evaluation of the activity we used DAS28 for patients with RA , BASDAI for patients with AS and DAPSA those with PsA. The statistical tests were carried with SPSS v.24.

Results

Out of 93 patients, included in our research, ADA were found in 7 patients (7,52 %) on month 6, another 6 patients (13,97%) on month 12 and 2 other patients (16,12%) on the 24th month since therapy initiation. The mean values of DAS28, BASDAI and DAPSA on 6,12,24 month in group A are significantly lower than those in group B, p=0.001.

Conclusion

Our results prove the correlation between the production of the antidrug antibodies and the increase in the disease severity , represented in the increase of the disease activity indexes-DAS28,BASDAI,DAPSA in patients with RA,AS,PsA.

AUTO1-0060
PREDICTION, MONITORING AND PREVENTION

TESTING FOR AUTOIMMUNE DISEASES IN DIABETIC PATIENTS AND THEIR SIBLINGS - NECESSITY OR A NEW TREND?

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Background

The autoimmune process involving pancreatic β cells can also affect other organs. The aim of this investigation was to assess the prevalence of some autoimmune endocrine disease and specific autoantibodies in pediatrics' patients with type 1 diabetes mellitus (T1DM) and their siblings.

Method

75 patients, 105 siblings and 77 healthy children were included. The occurrence of autoimmune thyroid diseases, Addison's disease, autoimmune hypophysitis were established with medical history, physical examination and study results. Glutamic acid decarboxylase antibodies (GADA), insulinoma-associated antigen 2 antibodies (IA-2Ab), zinc transporter 8 antibodies (ZnT8Ab), thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), thyrotropin receptor antibodies (TRAb), anti-adrenocortical antibodies (AAA) and antipituitary antibodies (APA) were measured.

Results

Associated autoimmune diseases was diagnosed in 21,3% of T1DM patients, Hashimoto's thyroiditis (HT) was the most prevalent. Anti-thyroid antibodies, APA and AAA were detected in 17,3%, 4%, and 1,3% patients, respectively. Co-occurrence of islet cell and other autoantibodies was noted in 20% of T1DM patients. HT was observed in 6,7% of siblings children with T1DM. T1DM – associated antibodies as well as anti-thyroid antibodies, AAA and APA were detected in 12,4%, 9,5%, and 5,7% of subject, respectively. Co-occurrence of at least two organ-specific antibodies was observed in 6,7% of siblings.

Conclusion

Both T1DM patients and their siblings are at increased risk of other autoimmune diseases. Screening for T1DM as well as autoimmune thyroid and adrenal diseases is advisable for type 1 diabetes patients and for their siblings.

AUTO1-0773
PREDICTION, MONITORING AND PREVENTION

FOLLOW-UP TO 20 YEARS OF THE CHILDREN OF PATIENTS WITH AUTOIMMUNE DISEASES

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Background

Objective
To describe the findings found in the children of patients with active or non-active autoimmune diseases during pregnancy, at a follow-up of 20 years.

Method

Material and methods We collected the information of patients with autoimmune diseases (Antiphospholipid Syndrome, Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis) with a history of pregnancy with live product, from January 1997 to July 2017, and who continue in control in rheumatology. They were contacted by telephone between January and July of 2017, to quote them for consultation to carry out a survey.

Results

Results We contacted 115 patients, with diagnostico f autoinmune diseases: Antiphospholipid Syndrome, 91 patients, SLE in 15 (6 with concomitant antiphospholipid) and 10 with Rheumatoid Arthritis. 3 patients had twin pregnancies
At the time of the interrogation the age range of the children was between 2 months and 14.16 years. 65% were female.
3 daughters of patients with SLE, consulted (between 7 and 16 years old) for arthralgia, treated with NSAIDs with improvement. 1 presented positive antinuclear antibodies, leukopenia and polyarthritis for which they received treatment with hydroxychloroquine for 1 year with improvement of symptoms, currently asymptomatic. 4 daughters have Raynaud's phenomenon, without other clinical or paraclinical alterations. 5 has antinuclear antibodies. None have a diagnosis of autoimmune disease and the psychomotor development is normal.

Conclusion

Conclusions In long-term follow-up, at 20 years, we only find non-specific symptoms: arthralgias, leukopenia and autoantibodies in 11.3%. It is important to follow-up these children to detect early signs and symptoms of autoimmune diseases.

AUTO1-0622
PREDICTION, MONITORING AND PREVENTION

MMP3 IS A RELIABLE MARKER FOR DISEASE ACTIVITY, RADIOLOGICAL MONITORING, DISEASE OUTCOME PREDICTABILITY AND THERAPEUTIC RESPONSE IN RHEUMATOID ARTHRITIS

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Background

Screening the serological markers in rheumatoid arthritis (RA), it appears that the Matrix metalloproteinase-3 (MMP3) was extensively studied, namely in disease activity reflection, monitoring progress and therapeutic responsiveness, that did not gained enough attention by the professionals. The aims being to update on the MMP3 in RA and explore its place in RA disease predictability, activity monitoring and response to various therapeutic modalities.

Method

A search algorithm, covering the period 1990-2017, using the key words: “matrix metalloproteinase-3” or “mmp3” AND “rheumatoid arthritis” or “RA” was conducted on PubMed, Medline, EMBASE, Scopus, and the Cochrane Database of Systematic Reviews, to identify the most relevant publications.

Results

82 publications were identified**.** Table 1 summarizes MMP3 levels positive correlations with RA disease activity, radiological damage, outcome disease predictability and drug therapy responsiveness.

RA aspects	No of publications	Years range	No of patients
Disease activity	19	1998-2017	1588
Radiological damage	17	1999-2016	2187
Predictability of disease outcome	15	2000-2016	2414
Drug responsiveness	19	1997-2016	1053

Conclusion

MMP3 is an enzyme that is actively involved in joint destruction in RA patients. Screening the last three decades, it appears that serum levels of MMP3 reflects positively and significantly rheumatoid arthritis disease activity, joint and bone injury, radiological erosion, predict disease outcome and drug responsiveness. It should be embedded in the routine assessment and monitoring and accompany therapeutic modalities, in rheumatoid arthritis medical management.

AUTO1-0408
PREDICTION, MONITORING AND PREVENTION

CORRELATION OF PARATHORMONE AND VITAMIN D3 VALUES IN FEMALE SAMPLES AND THEIR SEASONAL VARIATION DURING TWO YEARS PERIOD

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Background

To determine the correlation between parathormone and vitamin D3 and their seasonal variation

Method

Our material consisted of 1110 samples of women which were isolated from all clinics and outpatient departments of our Hospital during two year period (2015-2016). Parathormone levels were determined at the immunological analyzer ARCHITECT plus ci8200, Abbott (n.r 15-65 pg/ml) while the levels of vitamin D3 at COBAS e411 analyzer, Roche Diagnostics (n.r 20-60 ng/ml).The study of the correlation was made according to seasonal criteria.

Group A (Winter) 600 women, Group B (Summer) 510 women.

Results

At group A 40 women (6,66%) were found with vitamin D3 levels <3 ng/ml, 312 (52%) with levels <20 ng/ml, 246 (41%) with levels 20-60 ng/ml and just 2 (0,33%) with high levels >60 ng/ml. At group B 6 the corresponding values are 60 women (11,76) with vit D3<3 ng/ml, 284 (55,58) with levels <20 ng/ml, 164 (32,1%) with levels between 20-60 ng/ml and 2 (0,39%) with levels >60 ng/ml. The correlation of parathormone and vitamin D3 values has as follows:

Group A

Vit D3 (ng/ml)	Parathormone (pg/ml)		
	<65	65-100	>100
<3	2 (5%)	12 (30%)	26 (65%)
<20	70 (22.4%)	84 (26,3%)	158 (50,6%)
20-60	94 (38.2%)	66 (26,8%)	86 (34.3%)
>60	2 (0,33%)		

Group B

Vit D3 (ng/ml)	Parathormone (pg/ml)		
	<65	65-100	>100
<3	4 (13.33%)	2 (3.33%)	50 (83.33%)
<20	60 (21.12%)	36 (12.67%)	188 (66.19%)
20-60	54 (32.92%)	44 (26.82%)	66 (40.24%)
>60	2 (0,39%)		

Conclusion

No remarkable change in levels of vitamin D3 and parathormone was observed in relation to the season.At the lowest levels of vitamin D3 <20 ng/ml the majority of women presented parathormone levels >100 pg/ml at both of seasons.

AUTO1-0362
PREDICTION, MONITORING AND PREVENTION

EFFECT OF THE MINIMALLY MODIFIED LOW DENSITY LIPOPROTEIN CHOLESTEROL ON ATHEROSCLEROSIS PROGRESSION

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Background

Low density lipoprotein (LDL) cholesterol is a major risk factor in the pathogenesis of atherosclerosis. Circulating LDL invades the arterial wall and undergoes modifications such as oxidation. This particle can be oxidized into two different stages. First, minimally modified low density lipoprotein (mm-LDL) and fully oxidized-LDL. The fully oxidized-LDL is frequently found to be involved in the atherosclerosis progression. However, there are only a few studies regarding the role of the mm-LDL on this process. The aim of this study is to search for functional roles of the mm-LDL on atherosclerosis progression.

Method

Effect of the different type of LDLs on cellular expression of matrix metalloproteinases (MMPs) was observed using phorbal-12-myristate 13-acetate (PMA) activated THP1 cell as a model.

Results

Foam cells were induced by co-cultivation of the generated macrophages with LDL, mm-LDL, or ox-LDL. The intracellular lipid droplets of the foam cells were visualized by Oil Red O staining and observed under inverted light microscope. MMPs analysis using RT-PCR revealed that mRNA level of MMP-1, 2, 9, 12, 14, and 16 were increased once the degree of oxidation increased. Gelatin zymography analysis showed that an active form of MMP-2 was increased when the oxidation degree was increased, whereas MMP-9 activity was weak.

Conclusion

In conclusion our primary results suggested that mm-LDL is involved in the development of atherosclerotic plaque and rupture. However, its effect is less than the fully oxidized LDL. Further investigations are underway.

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AUTO1-0195
PREDICTION, MONITORING AND PREVENTION

VALUE OF THE DETERMINATION OF ANTIPLA2R ANTIBODIES IN THE MONITORING OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

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Background

AntiPLA2R antibodies (antiPLA2R-ab) appear to be very good biomarker for diagnosis of Idiopathic Membranous Nephropathy (iMN). Although preliminary data suggest that antiPLA2R-ab titre correlates with disease activity, there is discrepancy in the results.

Objective: to evaluate the diagnostic efficacy of the determination of antiPLA2R-ab in the diagnosis of iMN as well as the correlation with the disease activity in our population.

Method

Retrospective study of 184 patients at the time of diagnosis with antiPLA2R-ab request during 5 years.

Patients were classified in two groups according to the diagnosis by renal biopsy: 50 iMN, and 134 other diagnostics. AntiPLA2R-ab detection was performed using transfected cell-based indirect immunofluorescence (IIFT, Euroimmun).

In the patients diagnosed of iMN with positive antiPLA2R-ab at diagnosis or during follow-up (n= 31) values of creatinine clearance and 24-hour proteinuria are reported as clinical activity markers.

Statistical analysis were performed SPSS 20.

Results

Values of diagnostic efficacy of the determination of antiPLA2R-ab in the diagnosis of iMN in our population is shown in Table1.

Eight patients with diagnosis of iMN and antiPLA2R-ab negative turn into positive during their follow-up.

We find no correlation between 24-hour proteinuria (ρ spearman=0.094, p=0.354) or creatinine clearance (ρ spearman=0.094, p=0.445) and antiPLA2R-ab titre.

Conclusion

In our population, AntiPLA2R-ab present an elevated specificity that allows to avoid biopsies. In our study, no correlation is detected between antiPLA2R-ab titre and renal function parameters studied, so that serial determinations of antiPLA2R-ab titre (IIFT) don´t seem to be necessary for the follow-up of the disease.

AUTO1-0612
PREDICTION, MONITORING AND PREVENTION

THE PROGNOSTIC ROLE OF ADALIMUMAB THROUGH LEVELS IN CHRON'S DISEASE

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Background

There are no studies showing the ability of trough adalimumab levels to predict the long-term disease behavior in Crohn's disease patients.

The objective of the study was to prove the ability of trough adalimumab levels of predicting the long-term clinical course in Crohn's disease patients naïve to anti-TNF.

Method

We conducted a double blind, prospective, monocenter, observational study. The adalimumab trough levels and anti-adalimumab antibody titers were randomly assessed (Immundiagnostik ELISA) the day before the administration of the drug, together with C-reactive protein (CRP) and fecal calprotectin.

Results

Adalimumab and anti-adalimumab antibody trough values higher than 0.65 µg/ml and lower or equal to 0.1 AU/ml, respectively, predicted remission / mild disease activity ten months after the dosage (AUC: 0.85, $P < 0.0001$ and 0.82, $P = 0.0001$, respectively). In all patients who developed antibodies against adalimumab (antibody trough level > 0.1 AU/ml), the adalimumab trough level resulted under the threshold of 1.9 µg/ml. Consistent with the clinical disease activity, the fact that a statistically significant negative correlation was found between the adalimumab trough levels and the CRP and the calprotectin at the time of the biological drug dosing, shows that a low serum drug level is insufficient to control the inflammation

Conclusion

For the first time, our data demonstrate the ability of both adalimumab and anti-adalimumab antibody trough levels to predict the disease course at almost one year after the laboratory assessment. Further investigation in a large cohort and a correlation with the mucosal healing would be of benefit.

AUTO1-0656
PREDICTION, MONITORING AND PREVENTION

THE TEMPORAL EVOLUTION OF ANTI-INFLIXIMAB ANTIBODIES IN TREATED PATIENTS

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Background

All biological drugs have the potential for immunogenicity that primarily manifests in the production of anti-drug antibodies (ADA) that are associated with lower serum drug levels, infusion reactions and with loss of response.
The objective of this study is to evaluate the relationships among the kinetics of ADA, drug and clinical outcomes in infliximab-treated patients.

Method

Eighty-nine patients were included and sera obtained before each infusion were collected longitudinally during nine years and retrospectively analysed for Iinfliximab and ADA levels by a commercial kit ELISA.

Results

Thirty-nine out of 89 patients (43.8%) developed ADA. In the great majority (83.3%) of ADA+ patients, the ADA onset was restricted to the first drug infusions. ADA were detectable at several time points (till more than six years) in patients with ongoing therapy, without any drop of their titre. Drug levels resulted inversely related to the amounts of ADA, declined till their disappearance before the ADA onset and were consistently undetectable in the subsequent longitudinal samples of ADA+ patients. ADA were yet detectable after two years after the discontinuation of therapy. ADA onset preceded the hypersensitivity reactions and their levels were higher than those from loss of response or tolerant patients. HRs were more frequent in patients who started the second cycle of therapy after discontinuation and the ADA onset occurring after the first infusion very tight with HR.

Conclusion

This study provides evidence that onset and kinetics of ADA are restricted to the first 12 months of therapy and are temporarily related to clinical outcomes.

AUTO1-0666
PREDICTION, MONITORING AND PREVENTION

IGG4 ANTI-INFLIXIMAB IN TREATED PATIENTS

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Background

The use of infliximab (IFX) carries potential risk of immunogenicity with the production of anti-drug antibodies (ADA), leading to loss of response or acute infusion reactions.
The objective of this study was to analyse the production of IgG4 anti-IFX in a cohort of IFX-treated patients and to evaluate their relationship with ADA and clinical outcomes.

Method

ADA were detected by using a standardized bridging ELISA in the serum of a cohort of 222 treated patients with different diseases. The same samples were further analyzed for IgG4 anti-IFX using ImmunoCAP Specific IgG4. A longitudinal evaluation with both assays was also performed in 38 IFX-treated patients.

Results

ADA developed in 80 out of 222 (36%) IFX-treated patients. Detectable levels of IgG4 anti-IFX were shown in 59 out of 222 (26.6%) treated-patients. Fifty-seven out of 80 ADA+ patients developed detectable levels of IgG4 antibodies. Two IgG4-positive but ADA negative patients were identified. Serum levels of IgG4 positively correlated with the serum levels of ADA. Both reactive and non responder patients showed higher percentage of IgG4-positivity than tolerant patients. The longitudinal analysis of IgG4 anti-IFX showed that the majority of patients tested positive for IgG4 after few infusions.

Conclusion

This study indicates that IgG4 anti-IFX antibodies frequently developed in treated patients and that a large part of ADA-producing patients produces IgG4 anti-infliximab. A stronger IgG4 response toward IFX is detectable in patients with a previous hypersensivity reaction to the drug or with a loss of response to the treatment.

AUTO1-0728
PREDICTION, MONITORING AND PREVENTION

"SINE" RHEUMATIC SYNDROMES

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Background

Rheumatic diseases are characterized by a very diverse, multi-symptom clinical picture. Individual entities are identified on the basis of specific classification or diagnostic criteria. However, in some cases, the diagnosis is suggested despite the absence of symptoms that are key to the disease. Clinical practice indicates that missing symptoms may appear later or not at all. This is the reason for the creation within clinical entities of conventional subgroups of a similar course, clinical manifestation and prognosis. Different subgroups are also characterized by a different response to therapy, hence they require specific therapeutic recommendations. The group of rheumatic diseases referred to as "sine syndromes" is characterized by the lack of certain symptoms needed to recognize their parent clinical entity,ie.systemic sclerosis sine scleroderma. The state of knowledge on the clinical picture and management of patients with some of these diseases will be presented.

Method

xxx

Results

xxx

Conclusion

xxx

AUTO1-0720
PREDICTION, MONITORING AND PREVENTION

THE EFFECTS OF GOLIMUMAB ON CLINICAL AND PATIENT CENTRIC OUTCOMES AMONGST RHEUMATOID ARTHRITIS (RA) PATIENTS IN GREECE

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Background

Real world evidence regarding the clinical effectiveness and patient's experience associated with the use of Golimumab (GLM) is limited. The present post-hoc sub analysis of RA patients enrolled in a Greek observational study (PANORAMA) who were treated with GLM, was conducted.

Method

254 patients with RA (who initiated or switched to anti-TNF at enrollment) were included during 2014-16. HAQ-DI was used for the Quality of Life evaluation, DAS-28 ESR score for the clinical effectiveness and the TSQM for the satisfaction with treatment. Persistence to treatment was additionally assessed. The observational period was 12 months (12m).

Results

A total of 139 patients were treated with GLM; mean age was 59.1 ± 14 years, 84.9% were female, 61% were biologic naïve. Mean DAS-28 ESR and HAQ-DI scores at enrollment were 5.5 ± 1 and 1.4 ± 0.6 respectively, mean disease duration was 7.1 ± 6.6 years with 54.4% of patients being seropositive (RF (+):51.1%, Anti-CCP (+): 40.8%). At 12m 54% demonstrated a good EULAR response, 38% were in DAS-28 ESR remission (73% of patients with good response at 3m retained their responder status at 12m) and 35% were in HAQ-DI functional remission. The 12m Global Satisfaction and persistence rates were 71.2% and 76.7% respectively. DAS-28 ESR score decreased throughout the 12m follow up period (5.5 versus 3.2, $p<0.001$).

Conclusion

GLM appears to be an effective treatment for patients with RA, associated with high rates of good EULAR responses, high DAS-28 ESR remission rates and improvement in patient-reported measures.

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AUTO1-1043
PREDICTION, MONITORING AND PREVENTION

ANQUILOSANT SPONDILITE: DEFINING THE CHARACTERISTICS OF A POPULATION

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Background

Anquilosant spondilite is a chronic inflammatory rheumatic disease, which is part of the seronegative spondyloarthropathies affecting the axial skeleton and, to a lesser degree, peripheral joints and extra-articular organs.

Spondyloarthropathies are characterized by inflammation of synovium and enthesis, with axial involvement and oligoarticular peripheral arthritis.

Nighttime pain, morning stiffness and, in later stages of the disease, functional disability are the most frequent complaints.

It is a disease may result in a high functional disability if not treated in a timely and appropriate manner.

Physical Medicine and Rehabilitation plays an important role in maintaining the function and quality of life of these patients.

Method

The authors performed a retrospective analysis of the population belonging to the autoimmune disease consultation file for a total of 30 patients.

Results

In this analysis they characterized this population with respect to sex, demonstrating that half of the patients are female and half are male, with respect to age: 1 patient is between 18 - 30 years, 10 patients are between 31 - 40 years, 9 are between 41 - 50, 7 are between 51 - 60 years and 3 are between 61 and 80 years old, on therapy: 15 are being treated with NSAIDs, 10 are undergoing biological therapy. 40% are being followed in Physical Medicine and Rehabilitation and 10% in Pain Consultation, no patient was discharged from the consultation in the last 5 years.

Conclusion

The aim of this analysis was to know the prevalence of the main clinical and pathological characteristics of these patients.

AUTO1-0016
PREDICTION, MONITORING AND PREVENTION

DIAGNOSTIC VALUE OF 14-3-3 ETA PROTEIN LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background:

14-3-3η is a protein that is overexposed in serum and joint fluid of patients with rheumatoid arthritis (RA) and may represent a diagnostic biomarker for RA. We assessed the prevalence and levels of 14-3-3η in patients with RA and with other rheumatic diseases.

Methods:

Serum levels of 14-3-3η were measured in 45 patients with early non-treated RA that lasted less than 1 year, 101 patients with different rheumatic diseases and 66 healthy subjects. The disease control group included 33 patients with systemic lupus erythematosus (SLE), 44 patients with ankylosing spondylitis (AS) and 24 psoriatic arthritis (PsA) patients. All of the sera samples were evaluated by JOINT stat 14-3-3η ELISA test kits (Augurex Life Sciences Corp.). The cut-off was defined as 0.19 ng/ml.

Results:

Median 14-3-3η levels were significantly higher in the early RA groups (0.25 ng/ml) compared to the control groups: SLE (0.01 ng/ml, $p < 0.0001$), AS (0.05 ng/ml, $p < 0.0002$), PsA (0.01 ng/ml, $p < 0.0001$) and healthy subjects (0 ng/ml, $p < 0.0001$). Increased 14-3-3η levels were found in 58% of the early RA patients and they were significantly higher than in the control groups (SLE: 9%, $p < 0.001$; AS: 27%, $p < 0.002$, PsA: 12.5%, $p < 0.001$; healthy subjects: 5%, $p < 0.001$).

Conclusion:

The concentration of 14-3-3η protein may be used to distinguish between patients with early RA and patients with other rheumatic diseases and serve as an additional biomarker in the diagnosis of RA.

AUTO1-0249
PREDICTION, MONITORING AND PREVENTION

NEW SCORING SYSTEM FOR PREDICTION OF TNF INHIBITORS RESPONSE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background

Biologic treatment improve outcome of the patients with rheumatoid arthritis(RA). However, the selection of appropriate biologics treatment in individual patients is still challenging. We aim to make a predictive scoring system regarding treatment response of TNF inhibitors (TNFi) for RA management.

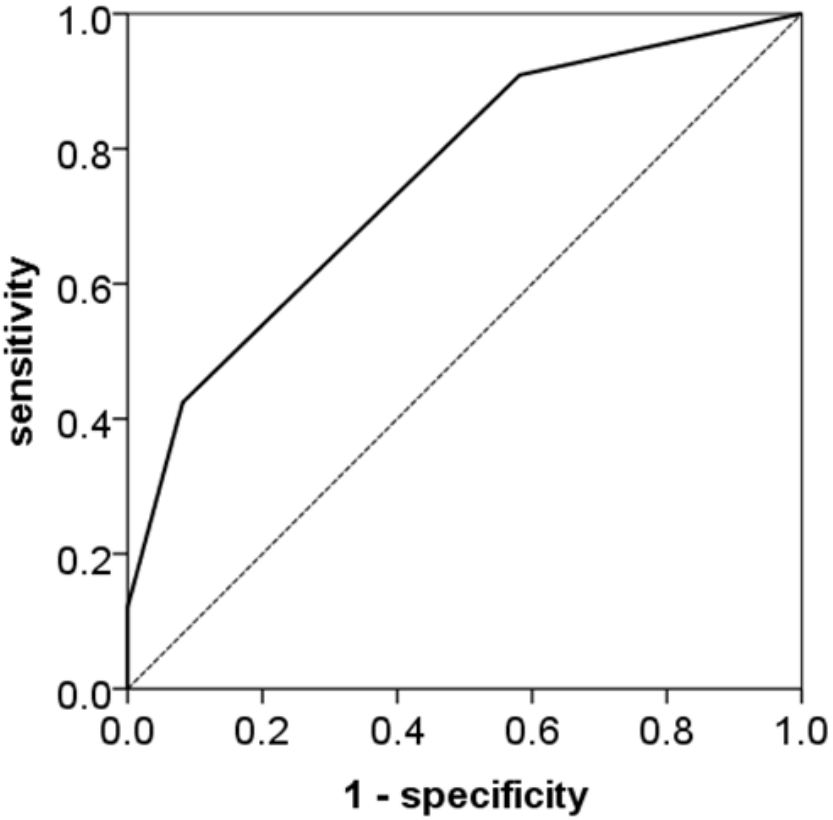
Method

This retrospective observational study was conducted by 4 sites and comprised RA patients treated with TNFi (certolizumab-pegol (CZP) or adalimumab (ADA)) from July 2013 to February 2017. Risk factors of treatment failure with TNFi were analyzed and scoring system was established. Score was calculated according to the number of risk factors. Validation of the scoring system was performed using ROC analysis at 24 weeks (24w) in patients treated with TNFi. Additionally, we evaluated the efficacy of tocilizumab (TCZ) against TNFi resistance group predicted by this scoring.

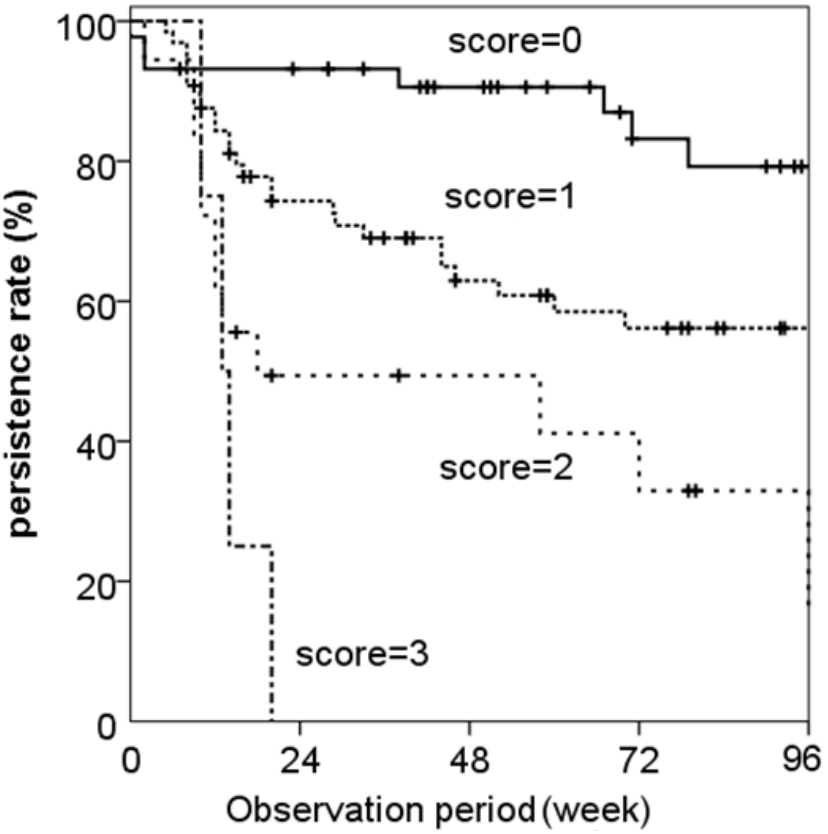
Results

One hundred thirty-one patients were enrolled. Corticosteroid user (PSL>5mg/day, p=0.009), DAS28-CRP>4.0 at baseline (p=0.005) and past history of biologic use (p=0.006) were found as independent predictive factors of TNFi discontinuation. AUC of ROC curve was 0.755 (95%CI: 0.659-0.851) [Figure1] and the persistence rates at 24w were shown in each score [Figure2]. Using a threshold of ≤ 1 score, sensitivity was 42% and specificity was 92%. In patients with ≥ 2 score, TCZ group (n=61) has longer persistence rate as compared with TNFi group (n=22, p<0.001).

[Figure1]



[Figure2]



Conclusion

High score predicted lower response rate of TNFi in score-dependent manner. TCZ is available for the high scored patients.

AUTO1-0425
PREDICTION, MONITORING AND PREVENTION

PREVALENCE AND AGE RELATED VARIABILITY OF AUTOANTIBODIES SPECTRUM IN A COHORT OF GREEK HEALTHY ADULTS

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Background

The aim of this study was to investigate the prevalence of autoantibodies in 187 adults classified in 3 age groups: group I (18-40 years), group II (41-64) and group III (65-87). No autoimmune diseases were mentioned (only two women reported Hashimoto's thyroiditis diagnosis).

Method

The autoantibodies studied were anti-nuclear (ANA), anti-double stranded DNA (dsDNA), anti-neutrophil cytoplasmic (ANCA), anti-mitochondrial (AMA), anti-smooth muscle (ASMA), anti-liver/kidney microsomal type 1 (anti-LKM1) and anti-parietal cell (APCA), antibodies (abs). Indirect Immunofluorescence (IIF)* assay was *the method used initially* for abs testing and positive samples were further identified by Line Immunoassay (LIA).

Results

ANA were detected in 31 of 187 samples (16,6%), 25 out of 116 women (21,6%) and 6 out of 71 men (8,5%). In group I, 10 out of 67 (14,9%) samples, in group II, 12 out of 73 (16,4%) and in group III, 9 out of 47 (19,1%) were positive. Anti-dsDNA abs were not detected in any sample while in only one ANA positive sample anti-Mi-2 antibody was identified by LIA. Regarding ANCA, atypical pattern (a-ANCA) was observed in 5 (2,7%) samples. ASMA were detected in 3 samples (1,6%), APCA in 9 (4,8%), whereas AMA and LKM1 abs were not found in any sample. In the whole cohort studied the sera of 44 (23,5%) individuals had at least one autoantibody while 3 (1,6%) had more than one.

Conclusion

In conclusion, it is suggested that in Greek healthy adults the prevalence of autoantibodies in women is higher than in men and it increases with age.

AUTO1-0576
PREDICTION, MONITORING AND PREVENTION

BIOLOGICAL THERAPY PERSISTENCE

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Background

The treatment of patients with rheumatoid arthritis (RA) has substantially changed since the introduction of biological disease modifying anti-rheumatismal drugs (bDMARDs). However, patient response varies widely and drug changes are frequent in some patients. The cause of this variability may be linked to patient, disease and treatment factors.

Method

Our study will retrospectively review patients from our autoimmune disorder unit who fulfill the 2010 ACR/EULAR RA classification criteria and were treated with bDMARDs at any point of their disease course. Demographic and clinical features, namely disease presentation, activity and severity, extra-articular involvement the immunological profile will be recorded. Data concerning treatment length with each bDMARD, concomitant treatment with classical DMARDs, disease activity control under each drug and reasons for switching will be collected. Treatment adhesion information will also be derived from the study sample.

Results

Our study comprises 100 patients with variable follow-up and treatment lengths. Disease activity at presentation was high. About two-thirds of patients persist with the first bDMARD, while the remaining usually require multiple drug switches. Overall adhesion to treatment was good.

Conclusion

Our analysis will try to identify factors that influence bDMARD persistence in the treatment of RA and eventually infer individual treatment strategies. This will be evaluated not only through the length of treatment with disease control but also through the need to switch bDMARDs.

AUTO1-0298
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

LUPUS PREGNANCY: ACHIEVEMENTS AND OPEN ISSUES IN THE MULTIDISCIPLINARY MANAGEMENT

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Background

Our purpose was to analyze pregnancy outcome of patients with Systemic Lupus Erythematosus (SLE) by comparing the outcome of prospectively-followed pregnancies (PFP) and anamnestic pregnancies (AP); by comparing the outcome of PFP with the general obstetric population (GOP); by evaluating the disease features, maternal risk factors and treatment of pregnancies with adverse pregnancy outcome (APO) in PFP.

Method

94 SLE patients (135 pregnancies) were followed prospectively by multidisciplinary team. 33 AP in the same SLE patients and 3939 pregnancies among GOP were evaluated.

Results

The comparison between PFP and AP showed lower frequency of premature miscarriage and fetal death and higher frequency of live birth in the first group. As compared with GOP, SLE-PFP displayed similar rate of early miscarriage and fetal loss but higher frequency of preeclampsia, preterm birth and Caesarian section.
APO occurred in 17 (12.6%) of the 135 PFP. Despite the lack of statistical significance, there was a tendency toward higher frequency of anti-dsDNA positivity, history of lupus nephritis and triple anti-phospholipid antibody (aPL) positivity in pregnancies with APO (table 1). Analyzing treatment during pregnancy, the group with APO received higher

doses of prednisone and required higher use of immunosuppressants.

Table 1. General and SLE-correlated risk factors in 'APO' and 'without APO' groups

General risk factors	APO %	Without APO %	P value
Age >35 years	35,3	30,5	0,491
Hypertension	17,6	16,1	0,722
Diabetes mellitus	0,0	0,8	1,000
Obesity	11,7	5,9	0,712
Thyroid disease	0,0	5,9	1,000
Cigarettes smoking	41,2	20,3	0,187
SLEDAI>0	86,7	83,9	1,000
SLEDAI>6	14,3	14,8	1,000
dsDNA	84,6	62,6	0,172
Lupus nephritis	52,9	33,0	0,167
Low C3 and/or C4	50,0	54,6	0,790
Ro/SSA and/or La/SSB	53,8	41,9	1,000
aPL	64,6	51,6	0,278
Triple aPL	23,5	11,8	0,244
LAC	23,5	21,2	0,760
Previous thrombosis	0,0	3,4	1,000
Previous APO *	35,3	21,2	0,221

*APO were defined as premature miscarriage (<10^ weeks), fetal death (>10^ weeks), preterm delivery (<34^ weeks) with or without preeclampsia, HELLP Syndrome, perinatal death (<30^ day).

Conclusion

The outcome of PFP in SLE has dramatically improved, thanks to pregnancy planning, multidisciplinary management and close monitoring during pregnancy. The occurrence of APO was restricted to a minority of PFP (12,6%). SLE-PFP had similar rates of pregnancy losses as compared to GOP, but there are still open issues on some pregnancy complications that affect SLE patients more frequently.

AUTO1-1047
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

TH17 AND REGULATORY T CELL BALANCE IN PREGNANT PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS - PRELIMINARY RESULTS

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Background

In our work we characterized the Th17 and Regulatory T cell (Treg) balance during pregnancy in lupus patients.

Method

Observational, prospective study where obstetric and neonatal outcomes of a group of pregnant lupus patients were compared with a control group of healthy pregnant women. Analysis of blood lymphocytes subpopulations, including Treg ($CD4^+/CD25^{++}/foxp3^+$) and Th17 ($CD4^+/IL\text{-}17a^+$) cells, were performed in each trimester and postpartum by flow cytometry and correlated with clinical data.

Results

21 pregnancies were included, 10 lupus patients and 11 controls. In lupus group, mean maternal age was 33,0+/-2,45 years, 30% were primiparas and 30% had history of miscarriage. Mean gestational age at delivery was 38,1 weeks and mean newborn birthweight was 2965,0grs. No differences in these variables were found between groups. No preeclampsia or flares were diagnosed. Analysis of Treg cells showed a continuous increment in mean Treg count during pregnancy to postpartum. A significative higher number of Treg cells was found in pregnant lupus patients during all pregnancy and postpartum, except during the third trimester. Th17 cell count increased during the third trimester in the lupus patients. The ratio Treg/Th17 increased continuously during all pregnancy in lupus group, but not in the controls. This data represents a preliminary report of this study.

Conclusion

In this cohort of lupus pregnant patients, we found that, in the absence of adverse obstetric outcomes, the increment of Treg cells is significantly higher than in the control group. This reflects a significative difference in the Treg/Th17 ratio between these groups along the pregnancy.

AUTO1-1051
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

MANAGEMENT OF SEVERE BEHÇET'S DISEASE DURING PREGNANCY

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Background

Behçet's disease (BD) is a rare systemic vasculitis that seems to adversely affect pregnancy, notably, early pregnancy loss and fetal growth restriction (FGR).

Method

Description of the management of severe BD during pregnancy using an illustrative case report.

Results

We report the case of a 32-year-old woman with severe BD diagnosed at the age of 27 with recurrent history of oral and vulvovaginal ulcers, uveitis, pseudofolliculitis, erythema nodosum and acneiform nodules. This patient experienced 4 years of primary infertility with implantation failure of 6 cycles of *in vitro* fertilization (IVF). She was diagnosed with premature ovarian failure. Increasing dosages of prednisolone and azathioprine were required leading to the necessity of starting infliximab to achieve BD remission. After 2 cycles of infliximab, IVF with donor oocytes was performed and a twin pregnancy was achieved. During pregnancy, the initial treatment was aspirin, enoxaparin, prednisolone 10mg and 2 cycles of infliximab (at 9weeks and 17weeks of pregnancy). Despite this therapy, she experienced a continuous worsening of mucocutaneous symptoms, requiring increasing dosage of corticosteroids, a cycle of certolizumab therapy at 24weeks, high dose bolus of corticosteroids at 28weeks and 32weeks. At 33weeks, she was hospitalized because of severe FGR in both fetus and delivered 2 low-weight healthy newborns at 36weeks by caesarean section because of active vulvar disease. After delivery, the patient had significant symptomatic improvement.

Conclusion

BD may be the cause of implantation failure so disease control may be needed to achieve pregnancy. However, pregnancy itself may represent a challenge to symptomatic control in these patients.

AUTO1-0903
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

MATERNAL HUMAN NMDA RECEPTOR NR1 AUTOANTIBODIES IMPAIR NEONATAL BRAIN FUNCTION AND BEHAVIOR IN A MURINE MODEL OF GESTATIONAL TRANSFER

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Background

Pathogenic maternal anti-neuronal autoantibodies might impair brain development in the offspring, leading to neuropsychiatric abnormalities. Active diaplacental transport mechanisms together with a highly permeable blood-brain barrier enrich autoantibodies in the fetal brain, even despite asymptomatic mothers.

Method

We established a mouse model of gestational transfer with human recombinant antibodies against the NR1 subunit of the *N*-methyl-*D*-aspartate-receptor (NMDAR) and investigated effects on NMDAR function, brain development and behavior in the offspring.

Results

NR1 antibodies were massively enriched in the fetal brain, reduced synaptic NMDAR density, changed electrophysiological properties, increased mortality and affected physiological functions. In addition, behavioral abnormalities persisted into adulthood, including hyperactivity, lower anxiety and impaired sensorimotor gating.

Conclusion

Together with additional risk factors or stressful events, vulnerable brain circuits might facilitate delayed developmental disturbances. The findings define a novel mechanism for the development of neuropsychiatric morbidity which, after prospective confirmation, can lead to preemptive testing in women. Most importantly, it potentially offers causal therapeutic options to prevent developmental brain abnormalities and lifelong psychiatric morbidity in affected children.

AUTO1-0646
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

GENE EXPRESSION OF ABHD6, A KEY FACTOR IN THE ENDOCANNABINOID SYSTEM, CAN BE MODULATED BY FEMALE HORMONES IN HUMAN IMMUNE CELLS

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Background

One of the main risk factors for the development of an autoimmune disease is to be a woman. Much attention has been given to the involvement of female hormones in their etiology and sexual bias, although the mechanisms behind this potentially strong contribution in disease suscpetibility is poorly understood. *ABHD6* gene was recently identified as a risk factor for system lupus erythematosus and the risk was correlated with overexpression of the gene. ABHD6 is an enzyme that degrades the 2-AG, an endocannabinoid with immunomodulatory effects. Thus its degradation could contribute to immune dysregulation and development of autoimmune reactions. Sex hormones, such as estrogens, are believed to regulate important genes in the endocannabinoid pathway. However, no study was available regarding the effect of these hormones in human immune cells.

Method

In this study, *ABHD6* expression was evaluated by quantitative PCR in leukocytes from healthy male and females and in the presence of estrogen or progesterone.

Results

A statistical increase in *ABHD6* expression could be detected in women. In the presence of estrogen or progesterone, a statistical upregulation of *ABHD6* was observed, and in a sex-dependent manner, as only female cells responded to stimulation.

Conclusion

Our results suggest that female hormones can promote the overexpression of *ABHD6* in immune cells. This can potentially contribute to a pro-inflammatory scenario and partially explain the association of this gene in the development of LES, a highly female-biased disease.

AUTO1-0750
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

MODIFIED-RELEASE PREDNISONE SHOWS A FAVORABLE SAFETY PROFILE IN THE MANAGEMENT OF MODERATE-ACTIVITY SYSTEMIC LUPUS ERYTHEMATOSUS DURING PREGNANCY: A 4-YEARS CASE-CONTROL STUDY

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Background

Systemic lupus erythematosus (SLE) affects women of childbearing age. Prednisone is safely used, at low doses, during pregnancy. There are no data on modified-release prednisone (MRP) use during pregnancy: we aimed to investigate its administration.

Method

We retrospectively evaluated 10 pregnant SLE women. All the cases were taking low-dose MRP (5 to 7.5 mg/daily), from at least 6 months. They were matched to 10 controls, with the same features, but taking the IR formulation. Pregnancy outcomes; SLE disease activity (during pregnancy, SLEPDAI) and at baseline/post-partum (SLEDAI) score; patient's global assessment (VAS, mm); need of treatment changes (%) were assessed.

Results

MRP and IRP age and disease duration were superposable. SLEDAI at baseline was 2±0.5 among MPR and 2±0.8 among IR; SLEPDAI, 2±0.9 and 2±1.0 (p=ns). No major perinatal complications were detected. SLEDAI at postpartum was 2.3±0.8 in MRP and 4.3±0.5 in IR ($p<0.05$). Patients VAS (MRP vs IR) was 3±0.4 and 2±09 at baseline (p=ns); 2±0.6 and 4±0.7 during pregnancy ($p<0.05$) and 3±0.3 and 4±0.9 at postpartum ($p<0.05$). Treatment regimen changes involved 1/10 (0.1) MRP and 6/10 (0.6) IR women during pregnancy+postpartum ($p<0.001$).

Conclusion

Activity (SLEDAI) score was significantly higher at postpartum and treatment had to be increased in IR patients, to manage SLE. VAS, conversely, was significantly higher among IR, both during pregnancy and postpartum. Minor and expected complications rates did not differ between the two subpopulations. MRP treatment seems to be as safe, but more effective, in comparison to the standard IR one, during pregnancy of SLE-affected women.

AUTO1-0345
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

PSYCHOSOCIAL ASPECTS OF REPRODUCTIONAL LIFE IN WOMEN WITH SLE: A SYSTEMATIC REVIEW

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Background

Women with systemic lupus erythematosus (SLE) are at an increased risk of perinatal complications. Therefore, a specialized, suitable and multi disciplinary approach is essential for a good outcome. The objective of this study was to understand the psychosocial aspects of women of reproductive age with SLE, specifically involving pregnancy.

Method

A systematic review was designed. A search was performed using: Pubmed, CINAHL, Embase, Psycinfo, SCOPUS and web of Science, based on the searches: SLE, psychosocial aspects, pregnancy and puerperium, without publication period or language restrictions.

Results

Of 63 articles identified, six were selected for analysis. Semi-structured interviews with content analysis or cohort studies were used, from countries including Sweden, Italy, the United States and Korea. Three categories were emphasized: 1) Reception and education of pregnancy risk in women with SLE, generating the need for active participation in decision-making for family planning; 2) The intense desire for pregnancy, and the commitment with which women with SLE demonstrate when facing the risks associated with pregnancy; 3) The impact of the disease on family planning, with decreased desire to become pregnant in comparison to women without SLE.

Conclusion

The inherent struggle in whether to become pregnant is obvious, therefore an environment for psychosocial reception of women with SLE for decision making is paramount, providing the woman and her family a safe environment to face the choices needed for adequate family planning and pregnancy outcomes.

AUTO1-0350
PREGNANCY, SEX HORMONES AND AUTOIMMUNITY

PERCEPTIONS OF WOMEN WITH LUPUS IN A SPECIALIZED PRE NATAL SERVICE: A QUALITATIVE CLINICAL STUDY

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Background

Women with systemic lupus erythematosus (SLE) run the risk of pre natal complications, and family planning allows better outcomes. Understanding the characteristics of pregnancy experiences of women with SLE allows considerations to improve their pre natal care.

Method

This qualitative clinical study was designed to better understand the experiences and importance attributed to pregnancy by women with SLE. Semi-structured interviews were performed followed by thematic analysis. The pregnant women, all in their third trimester, were followed up in tertiary prenatal care in the Brazilian public health system. The study consisted of ten participants: five Caucasian and five non-Caucasian women; six related having a partner, while four were single; with an average of seven years of schooling; mean age of 26 years; mean gestational age of 34 weeks; and a mean time of disease diagnosis of nine years.

Results

Analysis revealed a lack of family planning and use of contraceptive methods by all participants, suggesting an important problem in the delivery of health care, particularly since this population represents a vulnerable group who need ongoing follow-up, therefore, an improved link between healthcare services and effective family planning is required.

Conclusion

To achieve this, strategic actions need to be elaborated and implemented for health professionals, with an active participation of women of reproductive age to establish treatment goals for disease control, as well as family planning, aiming to predict and hence, minimize prenatal risks.

AUTO1-0248
PROTECTIVE ANTIBODIES

THE PREVALENCE OF DFS70 AUTOANTIBODIES IN THE CONTEXT OF A ROUTINE ANA COHORT.

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Background

Dense Fine Speckled (DFS70) pattern on HEp-2 substrate is a common finding in clinical laboratory referrals. High prevalence of DFS70 autoantibodies in healthy population and general negative association with systemic Antinuclear Antibody (ANA)-associated autoimmune rheumatic disease (SARD/AARD) were reported. The aim of this study was to evaluate the prevalence of DFS70 autoantibodies and their association with other circulating autoantibodies in the context of a routine ANA referral cohort.

Method

Consecutive sera submitted for ANA screening were tested for anti-DFS70 antibodies by indirect immunofluorescence (IIF) (n=3551, 1030 men and 2521 women) then confirmed by Immunoblotting. In addition, following autoantibodies were analysed: anti-ENA, anti-dsDNA, -anti-TPO, anti-TG, anti-Tg, anti-APLA, anti-PCA, anti-AMA, anti-ASMA, anti-LKM.

Results

The frequency of anti-DFS70 antibodies was 1.80% in the whole population and 4.99% in the ANA-positive samples. A quantitative comparison between DFS70 IIF and Immunoblotting showed an excellent correlation between the two methods. Surprisingly the percentage of females anti-DFS70 positive (2.1%, 53/2521) was statistically significant higher then the percentage of males anti-DFS70 positive (1.1%, 15/1030). Of note, no concomitant autoantibodies were found in the DFS70-positive males group compared with DFS70-positive females group showing other serum autoantibodies in the 45% of cases.

Conclusion

The isolated anti-DFS70 reactivity in male population may represent an exclusive biomarker to predict the absence of other autoantibodies. On the contrary, the serological profile of DFS70-positive females required further investigations in order to define related clinical associations.

AUTO1-0437
PROTECTIVE ANTIBODIES

HELICOBACTER PYLORI CAG-A AND VAC-A SEROPOSITIVITY IN PATIENTS WITH PSORIASIS

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Background

An ongoing debate currently exists as to whether *Helicobacter pylori* (Hp) infection is related to the aetiopathogenesis of psoriasis (Ps).
Since CagA and VacA are the most virulent factors of Hp, we sought for serological evidence of anti-CagA and VacA antibodies in a well-defined cohort of Ps patients compared to their demographically matched healthy controls (HCs).

Method

A total of 93 serum samples (55 Ps and 68 HCs) were tested for anti-Hp antibodies by a westernblot/line immunoassay combination (Euroimmun, Lubeck, Germany).

Results

Hp seropositivity has comparable in Ps (43.6%) and HCs (48.5%). Overall, IgG anti-CagA and VacA were present in 45.5% and 3.6% Ps patients, respectively, compared to 70.9%, (p=0.006) and 5.9% (p=NS) HCs, respectively. Although the relative titres of antibodies against VacA in Ps and HCs did not differ, the titres of antibodies against CagA in Ps were lower than in HCs (34.63±39.41vs 53.81± 49.39 respectively, p=0.027).

Conclusion

Hp seropositivity is comparable between Ps patients and healthy individuals. The frequency, as well as the magnitude, of reactivity against CagA is significantly lower in Ps patients than in the controls dismissing a triggering effect of this microbial antigen in the immunopathogenesis of the disease.

AUTO1-0008
PROTECTIVE ANTIBODIES

THE PREVALENCE OF ANTI-DFS70 AMONG HIV POSITIVE INDIVIDUALS – A PROSPECTIVE STUDY

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Background

Anti-DFS70 is an antinuclear antibody directed against DFS protein which is produced in response to several stressful events. Since its discovery, this autoantigen- antibody complex has drawn the attention of many researchers yet many questions remain unanswered. The DFS protein is crucial for HIV integration into host DNA, however the relation between anti-DFS70 and HIV is unknown. A protective role of anti-DFS70 against HIV is possible, due to the competition of the HIV integrase, and the anti-DFS70 antibody have on the same target site on DFS70. The aim of the study was to assess the prevalence of anti-DFS70 in HIV positive individuals seeking for possible interrelation.

Method

A total of 100 HIV positive individuals followed by the HIV unit at the Sheba Medical Center were tested for the presence of anti-DFS70. A total of 92 non-HIV, randomly selected, were tested and compared as controllers. Chemiluminescence assay (CIA) by QUANTA Flash was performed to evaluate the presence of anti-DFS70.

Results

None of HIV positive individuals had a positive test for anti-DFS70 (0%) compared to 10 out of 92 non-HIV persons (10.9%).

Conclusion

This is the first study addressing the prevalence of anti-DFS70 in HIV positive patients. The prevalence of anti-DFS70 was found to be significantly lower in HIV positive individuals compared to non-HIV persons ($p=0.002$). The absence of anti-DFS70 in HIV positive subjects implies that individuals who lack these protective antibodies are susceptible to HIV infections.. Studies with larger populations are needed to confirm this hypothesis.

AUTO1-1065
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

RETROSPECTIVE ANALYSIS OF 30 PATIENTS WITH LIMITED CUTANEOUS SYSTEMIC SCLEROSIS FOR 20 YEARS

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Background

[Objectives] To evaluate complications and the prognosis in patients with limited cutaneous systemic sclerosis (lc SSc).

Method

[Patients] The background of 30 patients at the diagnosis was as follows, 29 females, mean 59.0 years old, mean duration after appearing Raynaud' phenomenon; 10.8 years, Sjogren's syndrome; 22, Primary biliary cirrhosis (PBC); 8, Pulmonary arterial hypertension (PAH); 3, Interstitial pneumonia diagnosed by chest X-ray film; 1.
[Methods] Organ involvements, survival rate and the cause of death were surveyed by medical records for 20 years.

Results

[Results] 1) Eight patients were transferred to other hospitals and unknown in details. 2) Two of three patients with PAH were dead and the other was transferred to the other hospital. Two patients were newly developed to PAH and one patient was dead of heart failure. 3) One of eight patients with PBC was dead of liver failure and three patients were transferred to other hospitals. One patient was newly developed to liver cirrhosis and dead finally.Eight patients were dead (mean 71.1 years old); 3PAH (mean 63.0 years old), 2 liver failure (mean 79.5 years old), 1 intrahepatic cholangioma (73 years old), 1 esophageal cancer (65 years old),1 cerebral infarction (83 years old).

Conclusion

[Conclusion]PAH and PBC are frequently overlapped in patients with lc SSc. It was reconfirmed that PAH was a serious complication.

AUTO1-0082
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

THE CORRELATION BETWEEN DISEASE SPECIFIC ANTIBODIES AND MICROVASCULAR DAMAGE IN SYSTEMIC SCLEROSIS

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Background

Microangiopathy, fibrosis and autoimmunity predominate in the pathophysiology of Systemic Sclerosis (SSc). While anti-Scl-70 and anticentromere (ACA) antibodies are useful in SSc diagnosis and classification, their association with the extent of SSc related microvasculopathy remains to be clarified.The aim of our study was to investigate the correlation between microangiopathy and disease spesific autoantibodies in SSc patients.

Method

SSc patients attended scleroderma clinic in our Department between September 2016 and June 2017 were enrolled. All patients assessed for antinuclear antibodies (ANA), anti-Scl-70 and ACA and underwent nailfold video-capillaroscopy (NVC) to evaluate microcirculation. The number of capillaries/mm^2 and capillarosscopic index CSURI were measured. Findings were also classified to the three scleroderma patterns (early, active, late). The correlation between capillaroscopic and laboratory findings was examined.

Results

Thirty-seven consecutive patients (36 female, mean age 55.2 ± 13 years) were studied. ANA were positive in 33 (89.1%). Positive anti-Scl-70 were recorded in 13 (35.1%) and ACA in 6 (16.2%) patients. The presence of positive anti-Scl-70 was related to a lower number of capillaries/mm^2 ($r= -0.573$, $p<0,001$), higher values of CSURI index ($r= 0.408$, $p=0.017$) and higher grade of vasculopathy according to the qualitative classification in the three capillaroscopic scleroderma patterns ($\chi^2= 9$, $p=0.011$). No significant correlations were found between the presence of positive ANA or ACA and the extent of microvascular damage.

Conclusion

The presence of positive anti-Scl-70 is associated with a more extensive microvascular damage in SSc providing a possible link between vasculopathy and autoimmune activation in this population.

AUTO1-0555
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

DIFFERENCES BETWEEN DIFFUSE AND LIMITED SYSTEMIC SCLEROSIS IN AUSTRIAN PATIENTS

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Background

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterized by the excessive production and accumulation of collagen and vasculopathy. This leads to sclerosis of the skin and changes in internal organs (lung, digestive tract, kidney, heart). The aim of our work was to compare clinical and laboratory parameters of patients with diffuse SSc with those of patients with limited SSc.

Method

The data were obtained from the network for SSc, which has been maintained at the Department of Dermatology at the Ordensklinikum Linz Elisabethinen in Upper Austria since 2006.

Results

Out of 58 patients with SSc, 33 patients were diagnosed with diffuse SSc (anti-Scl-70 antibodies were positive in 15 patients) and 25 patients with limited SSc (Cen-B-P antibodies were positive in 18 patients). Pulmonary arterial hypertension (PAH) was present in 33.3% of patients with diffuse SSc and in 23.5% of patients with limited SSc. Pulmonary fibrosis was found in 72.2% of patients with diffuse SSc and in 29.4% of patients with limited SSc. Esophageal hypomotility had developed in all patients with diffuse SSc and in 70.5% of patients with limited SSc. Raynaud's syndrome was present in all patients with diffuse and limited SSc. Digital ulcers were seen in 50.0% of patients with diffuse SSc and in 35.3 % of patients with limited SSc.

Conclusion

PAH, pulmonary fibrosis, esophageal hypomotility and digital ulcers occur more frequently in diffuse SSc than in limited SSc, while Raynaud's syndrome is equally common in both forms of SSc.

AUTO1-0759
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

BICD2 ANTIBODIES IS HIGHLY SPECIFIC FOR SYSTEMIC SCLEROSIS AND ASSOCIATED WITH THE PRESENCE OF CENTROMERE ANTIBODIES.

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Background

Systemic sclerosis (SSc) is an autoimmune, connective tissue disease of unknown etiology affecting multiple organs. Autoantibodies support in the diagnosis as well as provide information regarding the risk of organ involvement and prognosis. Anti-BICD2 has recently been discovered as a novel marker of SSc. We have investigated a large cohort of well characterized patients with autoimmune connective tissue diseases for the prevalence of BICD2 antibodies and potential clinical correlations in patients with SSc.

Method

A total of 467 subjects (121 systemic sclerosis, 78 idiopathic inflammatory myopathy and 141 systemic lupus erythematosus, 100 healthy donors) were tested for the presence of BICD2 and centromere autoantibodies by ELISA and LIA in accordance to the manufactures recommendation

Results

BICD2 antibodies was primarily found in the SSc patients with a sensitivity of 19,8% and a specificity of 98,8%. The positive and negative predictive values were 85,5% and 77,7%, respectively. All patients who were BICD2 antibodies positive were also positive for centromere antibodies.

A combined measurement of BICD2 and centromere antibodies increased the specificity for SSc and positive prognostic values to 100%. BICD2 autoantibodies positive patients were significantly older compared to patients who alone were centromere positive ($p = 0.0005$). No other association to clinical outcomes was found.

Conclusion

BICD2 autoantibodies are highly specific to SSc patients. Anti-BICD2 is associated with higher age but no other clinical correlations are found in this cohort. Anti-BICD2 could be a valuable tool in the challenging diagnosis of SSc, however, further analysis is warranted.

AUTO1-0100
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

NAIL INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Background

Nail involvement has rarely been recognized in systemic sclerosis (SSc). Indeed, only a few small series have assessed nail changes in SSc, most of which are case reports. The aims of the current case-control study were to: (1) determine the prevalence of fingernail changes in SSc; and (2) evaluate the correlation between fingernail changes and other features of SSc.

Method

In all, 129 patients with SSc and 80 healthy control subjects underwent routine fingernail examination.

Results

The prevalence of fingernail changes was 80.6% in SSc. Patients with SSc more frequently exhibited: trachyonychia ($P = .006$), scleronychia ($P < .0001$), thickened nails ($P < .0001$), brachyonychia ($P = .0004$), parrot beaking ($P < .0001$), pterygium inversum unguis ($P < .0001$), splinter hemorrhages ($P < .0001$), and cuticle abnormalities ($P < .0001$) than healthy control subjects. The presence of fingernail changes was associated with digital ulcers ($P < .0001$), calcinosis cutis ($P = .004$), and higher values of mean nailfold videocapillaroscopy score ($P = .0009$).

Conclusion

This study underlines that fingernail changes are correlated with more severe forms of SSc characterized by digital microangiopathy, including digital ulcers and calcinosis cutis. Nail changes should be systematically checked in all patients with SSc, and may be included in the American College of Rheumatology/European League Against Rheumatism classification criteria for SSc.

AUTO1-0101
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

LACTOSE MALABSORPTION IN SYSTEMIC SCLEROSIS

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Background

There are no studies on systemic sclerosis (SSc) assessing the relationship between food intake, especially lactose, and gastrointestinal dysfunction. The aims ot the study were to: 1) determine the prevalence of lactose malabsorption, using lactose breath test, in patients with SSc. To evaluate the correlation between lactose malabsorption and gastrointestinal involvement; and 2) predict which SSc patients exhibit lactose malabsorption.

Method

Seventy-seven consecutive Caucasian patients with SSc and 20 control subjects underwent lactose breath test. All patients also completed a questionnaire on digestive symptoms, and a global symptom score (GSS) was calculated.

Results

The prevalence of lactose malabsorption was higher in SSc patients than in controls (44.3% vs. 10%; P = 0.004). We observed a marked correlation between the presence of lactose malabsorption and: higher values of GSS (P < 0.0001); severe oesophageal (P = 0.018) and small intestinal (P = 0.04) motor disorders; and joint involvement (P = 0.019). Furthermore, in SSc patients with symptomatic lactose malabsorption, the median value of GSS of digestive symptoms was lower after initiation of lactose-free diet (P < 0.0001).

Conclusion

Our study underscores the fact that lactose malabsorption often occurs in patients with systemic sclerosis. Furthermore, our findings highlight the fact that lactose breath test is a helpful, noninvasive method, by identifying the group of patients with systemic sclerosis with symptomatic lactose malabsorption that may benefit from a reduction in lactose intake.

AUTO1-0102
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

PLASMA HEAVY METALS IN SYSTEMIC SCLEROSIS

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Background

The aims of the case control study were to assess the relationship of SSc related to exposure to heavy metals, and the the risk of SSc related to occupational exposure in male and female patients.

Method

From 2005 to 2008, 100 patients with a definite diagnosis of SSc were included in the study; 3 age, gender, and smoking habits matched controls were selected for each patient. All SSc patients and controls underwent quantification of heavy metal traces in plasma samples, using multi-element inductively coupled plasma mass spectrometry (ICP-MS).

Results

SSc patients exhibited higher median plasma levels of the following metals: antimony ($p<0.0001$), arsenic ($p=0.0008$) and thallium ($p<0.0001$). A marked association between SSc and occupational exposure was further found for: antimony ($p<0.0001$), arsenic ($p=0.0023$) and thallium ($p<0.0001$) in female patients.

Conclusion

The results suggest the association between SSc and occupational exposure to: antimony, arsenic and thallium. Occupational exposure should be systematically checked in all SSc patients at diagnosis.

AUTO1-0108
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

ASSOCIATION OF CADMIUM EXPOSURE WITH FEATURES OF SYSTEMIC SCLEROSIS

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Background

Occupational exposure is reported as playing a substantial causative role in systemic sclerosis (SSc). We sought to compare the characteristics of SSc in patients with and without occupational exposure to cadmium.

Method

In all, 100 patients with SSc were enrolled in this prospective study. An expert committee performed blind evaluation of occupational exposure to cadmium. All SSc patients also underwent detection and quantification of heavy metal traces in hair samples, using multi-element inductively coupled plasma mass spectrometry (ICP-MS).

Results

Patients exposed to cadmium more often exhibited: diffuse cutaneous SSc (p=0.04) and higher median values of Rodnan score (p=0.02). These patients also more frequently developed interstitial lung disease (p=0.02) and anti-Scl 70 antibody (p=0.04).

Conclusion

Exposure to cadmium is correlated with more severe forms of SSc characterized by: diffuse cutaneous involvement and interstitial lung disease. Occupational exposure to cadmium should be systematically checked in all patients with SSc, as exposed patients seem to develop more severe forms of SSc.

AUTO1-0501
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

STUDY THE EFFECT OF PROGESTERONE ON MMP7 AND AMP; MMP13 EXPRESSION IN LUNGS OF MOUSE MODEL OF SYSTEMIC SCLEROSIS

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Background

Gender medicine is a new era of science which focuses on the impact of sex hormones and gender on normal physiology, pathobiology and clinical features of diseases. In our previous study we showed that supra physiological dose of progesterone exacerbate the lung fibrosis in a mouse model of scleroderma. Matrix metalloproteinases are a group of enzymes which play a role in tissue remodeling and fibrosis. Whereas the abnormal expression of MMP2 and MMP9 are indicated in the pathogenesis of systemic sclerosis, fewer studies are done on MMP13 and MMP7 which are expressed by epithelial cells, fibroblasts and macrophages of the lungs. They are involved in the pathogenesis of COPD, IPF and different lung diseases therefore we aimed to investigate the effect of progesterone on the expression of these two enzymes in lungs of mouse model of scleroderma.

Method

Female mice received progesterone for 28 and 21 days in addition to 28 days bleomycin. On day 29 mice were sacrificed and the expressions of these two enzymes in lungs were analyzed by real time PCR.

Results

We found that bleomycin significantly downregulated the expression of MMP7 and MMP13 and co-administration of progesterone and bleomycin declined the expression of these enzymes but not in a significant manner.

Conclusion

While progesterone cannot reduce the expression of MMP7 and MMP13 in mouse model of lung fibrosis more investigation on other player of fibrosis are necessary

AUTO1-0495
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

THE EXPRESSION OF CCN1 AND ITS SPECIFIC INTEGRINS IN LUNGS OF MOUSE MODEL OF SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis is an autoimmune disease with vascular abnormalities, skin and internal organs fibrosis. This disease results from deposition of extracellular matrix in tissues. Member of CCN family perform their different functions through interactions with their specific integrins and proteoglycans in health and disease. Concerning the role and interaction of CCN1/ CYR61 with its specific integrin receptors in fibrosis exist paucity of information. Therefore we aimed to evaluate the expression of CCN1 and its related receptors in lungs of mouse model of systemic sclerosis.

Method

Mice received bleomycin for 28 days for induction of fibrosis. On days 10, lungs were removed from lethally anesthetized mice for measurement of hydroxyproline content, histochemistry staining with H& E, Masson trichrome and RNA extraction. Specific primer for CCN1, α_v, β_3, α_6, β_1 were designed and qPCR was performe

Results

Hydroxyproline assay and Masson trichrome staining of mice, indicated fibrosis on day 28 and even more fibrosis on day 35. The overall infiltrated cells to lungs were significantly increased on day 28

qPCR results showed increment of CCN1 and α_6 β_1 integrin genes on day 10 and their decline to normal level on day 28. The expression of integrin α_v didn't change at any of the assessment days**Conclusion**

The increase of CCN1 and its integrin's transcript on day 10 prior to establishment of fibrosis on day 28, may indicate the role of CCN1 as a profibrotic factor in the Lung, however further investigation at the level of protein seems to be necessary.

AUTO1-0530
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

USE OF PULMONARY ULTRASOUND FOR THE STUDY OF PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS: A SINGLE CENTRE EXPERIENCE

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Background

Systemic Sclerosis is a rare autoimmune disease characterized by a complex pathogenesis.

Interstitial Lung Disease and Pulmonary Arterial Hypertensio represent the major cause of death, so an early diagnosis and treatment of these manifestations are mandatory.

High Resolution Computed Tomography and Right Hearth Catheterization are respectively the gold standard for the diagnosis of ILD and PAH, but Pulmonary Ultrasound has been recently proposed to evaluate lung's involvement.

Method

With the aim to evaluate the possible application of pulmonary ultrasound in ILD and/or PAH in subjects affected by SSC, during 2017 we enrolled 33 patients. We evaluate clinical data (included mRSS, 6MWT), autoantibodies, NT-proBNP, hemoglobin, markers of renal function, CRP and ESR, instrumental data (HRCT, echocardiography, pulmonary function tests, videocapillaroscopy). The fibrotic pulmonary involvement has been assessed using the Warrick score applied to HRCT. All patients has been studied with a pulmonary ultrasound at the enrollment and with a mountly follow-up for 6 months.

Results

Skin and pulmonary fibrosis showed a strong correlation, as well as Warrick score and DLCO andthe same radiological score and ultrasonographic parameters such as pleural irregularities and B lines. In the subgroup of ILD patients, pleural alterations and B lines are related to ILD and particularly to fibrosis' worsening. In the subgroup of PAH subjects, only B lines are related to PAPs and may be predictor of clinical worsening.

Conclusion

According with our data, pulmonary ultrasound may be usuful not in the diagnostic process but in the clinical follow-up for the assessment of the pulmonary damage.

AUTO1-0261
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

THE ROLE OF ANTINUCLEAR ANTIBODIES IN VASCULAR LESION IN PATIETNTS WITH SYSTEMIC SCLEROSIS

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Background

Systemic sclerosis (SSc) is characterized by functional and structural changes in blood vessels. Clinical manifestations of SSc are the result of autoimmune reactions leading to pathological accumulation of collagen and the development of obliterating vasculopathy. The role of autoantibodies in the pathogenesis of vasculopathy has not been completely studied. The aim of our study was to assess the contribution of different antinuclear autoantibodies in vascular lesion in patients with SSc.

Method

133 patients (13 males, 119 females) with SSc were enrolled in the study. The presence of telangiectasias, digital tip ulcers, finger tip pitting scars, pulmonary hypertension were evaluated. The results of naifold videocapillaroscopy (NVC), the density of the capillary loops and the pattern were estimated, a semi-quantitative evaluation was carried out. Autoantibodies nRNP/Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl, Jo-1, CENP B, PCNA, dsDNA, Nukleosomes, Histone, Rib. P-Prot, AMA-M2, Ku, Th/To, NOR 90, Fibrillarin, RP155, RP11, CENP A were assessed.

Results

The median age was 52±12 years. The association between PM-Scl-antibodies and all NVC-characteristics ($p<0,05$), between CENT B-antibodies and the presence of telangiectasias, between PCNA-antibodies and the presence of digital tip ulcers was established ($p<0,01$). Also we found the links between Ku-antibodies and the presence of telangiectasias and the NVC-pattern ($p<0,05$ and $p<0,01$, respectively), the associations of Th/To-, RP155-antibodies with the NVC-pattern ($p<0,01$), NOR90-antibodies with the presence of telangiectasias ($p<0,05$).

Conclusion

We established the contribution of different autoantibodies in the pathogenesis of vascular involvement in patients with SSc.

AUTO1-0764
PULMONARY ARTERIAL HYPERTENSION AND SYSTEMIC SCLEROSIS

AUTOIMMUNE AND INFLAMMATORY DISTURBANCES IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS

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Background

The prognosis for patients with pulmonary arterial hypertension associated with systemic sclerosis (SSc-PAH) is significantly worse than for ones with other forms of PAH, and the cause of such difference is still unclear.

Method

The study includes 51 pts with SSc-PAH and 65 with SSc without PAH. Serum concentrations of the C-reactive protein (CRP), anticentromere antibodies (ACA) and antibodies to topoisomerase-I (Scl-70) were routinely measured. Statistical analysis includes univariable logistic regression, ROC analysis and Kaplan-Mayer method.

Results

ACA was associated with a 15.2-fold increased odds of developing PAH in SSc (OR 15.2, 95% CI 5.4-43.0), on the contrary, presense of Scl-70 associated with low risk of PAH (OR 0.5, 95% CI 0.01 to 0.21). The level of CRP correlated with WHO FC, right atrium pressure and 6-minute walk test distance. The Kaplan-Mayer analysis showed that pts with CRP level more than 4.75 mg/l at the time of diagnosis of PAH had a significantly lower survival rate (median 48 months) than pts with normal values (median 91 months) ($p<0.005$), with 67% sensitivity and 61% specificity.

Conclusion

SSc-PAH is a unique phenotype combining the manifestations of both SSc and PAH, the pathogenetic mechanisms of which modify the course of these states. An increase in the concentration of CRP, as well as the effect of its baseline level on survival rate, attests to the significant role of autoimmunity and inflammation in the pathogenesis of this fatal SSc complication.

AUTO1-0354
RITUXIMAB AND B-CELL DEPLETION THERAPY

THE EFFICACY OF RITUXIMAB IN REDUCING PROTEINURIA IN PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY

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Background

Idiopathic membranous nephropathy (IMN) is one of the leading causes of nephrotic syndrome (NS) in adults and may result in end-stage renal disease (ESRD). The severity of proteinuria determines the forecast IMN.

Method

In study were included 47 patients, 63.8% males; mean age 56.2±10.4 years. The duration of the NS was 3 to 20 months. Twenty-five patients were treated with corticosteroids combined with alkylating agents. Anti-CD20 monoclonal antibody Rituximab (RTx) therapy (375 mg/m^2 once weekly for 4 weeks) in 22 patients, 12 of them had of NS, resistant to prior standard therapy, and 10 patients with a relapse of NS that developed after 2-9 years. The effectiveness of the therapy was evaluated at 24 months by the status of remission as complete and as partial (proteinuria <0.3 and <3 g/24 h respectively).

Results

Proteinuria in patients treated corticosteroids combined with alkylating agents significantly decreased in 20 out of 25 (80%) patients, complete remission was achieved in 13 (65%) and partial remission in 7 (35%) patients. Seven patients (35%) who achieved remission had a relapse of NS, 2 (8%) patients had developed ESRD and 3 (12%) died of cardiovascular events. Remission was seen in 18 (81.8%) out of 22 of RTx treated patients, complete remission was achieved in 14 (63.6%) and partial remission in 4 (18.2%) patients. Four patients (18.2%) had ultimately progressive ESRD and 1 patient (4.5%) had relapse of NS.

Conclusion

The effectiveness of RTx is comparable to that of therapy corticosteroids combined with alkylating agents in patients with IMN.

AUTO1-0346
RITUXIMAB AND B-CELL DEPLETION THERAPY

RITUXIMAB ACTS AS A TRIGGER FOR INFECTION IN IMMUNOCOMPROMISED PATIENTS

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Background

Rituximab exhibits a reputation for good tolerance in treatment of both monoclonal hematological diseases (MHD) and autoimmune diseases (AID). Nevertheless, severe (SI) and opportunistic infections (OI) have been described after this treatment. Herein we studied the timing of SI and OI after rituximab therapy.

Method

Charts of patients treated with rituximab in our tertiary internal medicine department between 2007 and 2015 were retrospectively analyzed. OI and SI were defined according to the consensus recommendations published by Winthrop et al and the CTCAE definitions, respectively.

Results

One hundred and one patients received rituximab for either AID in 52.5% or MHD in 47.5% (median follow-up 30.4 months). Patients received a rituximab median cumulative dose of 4340mg [interquartile range: 2620-6160]. SI and OI occurred respectively in 94 and 21 cases, concerning 50 patients. Fourteen events were both SI and OI. Nineteen events were lethal (4 of those were OI). After last rituximab infusion, SI occurred after 1.18 [0.43-6.50] months and OI after 1.08 [0.72-19.87] months. Respectively, AID and MHD patients experienced SI in 32.1% and 60.4% cases (p=0.006) and OI in 15.1% and 22.9% cases (p=0.42). Factor associated with mortality were polymicrobial infection (p<0.001), MHD (p=0.035), use of steroids (p=0.003), last rituximab infusion within the last 3 months (p=0.009) and rituximab cumulative dose (p<0.001).

Conclusion

Severe and opportunistic infections occur early after rituximab infusion, as well as patients had received previous immunosuppressive therapies. Rituximab seems to act as a trigger for infection in the more immunocompromised patients. Larger studies are warranted to confirm these results.

AUTO1-1052
SLE, SJÖGREN'S DISEASE

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH SJOGREN'S SYNDROME

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Background

Sjogren's Syndrome (SS) is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, mainly lacrimal and salivary glands, associated with B-cell hyperactivity, producing autoantibodies responsible for extraglandular symptomatology. It can be primary or secondary. The etiology of primary Sjögren's syndrome is unknown. It is more common in women.

Method

Review of the clinical processes of patients with primary and follow-up SS in the department of autoimmune diseases, analyzing demographic, clinical characteristics and treatment.

Results

Total of 19 patients, 15 women and 4 men, median age of 45 years. Of the personal history it stands out: 42.1% had arterial hypertension, 31.5% diabetes, 74% dyslipidemia; 100% of the patients had xerophthalmia, 89% xerostomia, 37% pathological Schirmer test, 89% positive antibody anti-Ro/SSA, 31.5% pathological salivary gland biopsy (only 6 biopsies were performed). In regard to treatment 63% were medicated with steroids, 47.3% hydroxychloroquine, 52.6% nonsteroidal anti-inflammatory drugs, 0% with biologic treatment.

Conclusion

The analyzed patient group presents clinical and demographic characteristics similar to those described in the literature. However, few glandular biopsies were performed because of the lack of medical experience in our hospital. Its important to have a high level of suspicion to diagnose SS.

AUTO1-0300
SLE, SJÖGREN'S DISEASE

HIGH CLINICAL PERFORMANCE OF A NOVEL BEAD BASED ASSAY FOR THE DETECTION OF AUTOANTIBODIES TO RIBOSOMAL P PEPTIDE FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Autoantibodies targeting the ribosomal-P antigen are highly specific for systemic lupus erythematosus (SLE) and are detectable in about 10-30% of the patients. The major epitope has been identified in the C-terminal part of the Rib-P proteins. The objective of the present study was to analyze the prevalence of anti-Rib-P antibodies in SLE using a novel fully automated bead based immunoassay.

Method

Sera from SLE patients (n=294), from individuals with various other diseases (n=478) and from apparently healthy blood donors (n=66) were tested for anti-ribosomal P antibodies by a novel fully automated bead based immunoassay (research use only, Inova Diagnostics). A reduced number of samples were also tested by ELISA (QUANTA Lite Ribosomal P) for comparison studies. Statistical analyses were done with Analyse-it® software.

Results

In the cohort tested with both methods, the sensitivity of anti-Rib-P antibodies measured by the novel assay was 25.0% and therefore significantly higher than using the ELISA (13.8%), at the same specificity of 98.3% (see table).

When SLE patients were compared to controls by ROC analysis, the area under the curve values were: 0.81 (95% CI 0.78-0.86) for the novel assay and 0.66 (95% CI 0.61-0.72) for ELISA (p=0.0026). In the entire cohort, the sensitivity for anti-Rib-P was 22.1% (95% CI 17.7-27.2%) with a disease specificity of 97.9% (95% CI 96.2-98.9%).

	Ribo-P ELISA	Ribo-P Bead based Assay
Sensitivity (95% CI)	13.8 % (9.2-20.2)	25.0% (18.8-32.4)
Specificity (95% CI)	98.3% (95.8-99.4)	98.3% (95.8-99.4)
LR+ (95% CI)	8.3 (3.1-22.8)	15.1 (5.7-39.9)
LR- (95% CI)	0.9 (0.8-0.9)	0.8 (0.7-0.8)
OR (95% CI)	9.5 (3.3-27.0)	19.8 (7.1-54.4)

Conclusion

Anti-Rib-P antibodies measured using the novel bead based assay showed superior performance when compared to ELISA. The high sensitivity and specificity of anti-Rib-P antibodies provides added value to the classification criteria markers anti-dsDNA and anti-Sm.

AUTO1-0310
SLE, SJÖGREN'S DISEASE

ANTI-SM ANTIBODIES MEASURED BY A NOVEL SMD1 PEPTIDE BEAD BASED ASSAY EXHIBIT GOOD CLINCIAL PERFORMANCE AS AN AID IN THE DIAGNOSIS OD SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Autoantibodies targeting the Sm antigen are highly specific for systemic lupus erythematosus (SLE) and are detectable in about 10-30% of the patients. The major epitope has been identified in the C-terminal part of the SmD protein family. The objective of the present study was to compare the diagnostic utility of antibodies against an SmD1 derived peptide with those reacting with the entire native Sm antigen.

Method

Sera from SLE patients (n=395), from individuals with various other diseases (n=918), and from apparently healthy blood donors (n=116) were tested for anti-Sm antibodies by a novel fully automated bead based immunoassay (research use only, Inova Diagnostics) using native purified Sm proteins and an SmD1 derived peptide. Statistical analysis (Fisher exact test, receiver operating characteristics (ROC) analysis) was done with ANALYSE-IT Version 4.90.1.

Results

When SLE patients were compared to controls by ROC analysis, the area under the curve value was similar for the two antigens: 0.69 (95% CI 0.65-0.71) for SmD1 peptide and 0.70 (95% CI 0.67-0.73) for the native Sm antigen. The correlation between the antigens was 0.79 (95% CI 0.77-0.81) using Spearman analysis.

	SmD1 peptide	Native Sm proteins
Sensitivity (95% CI)	20.5 % (16.8-24.8%)	17.7% (14.3-21.8%)
Specificity (95% CI)	97.2% (96.0-98.0%)	97.1% (96.0-98.0%)
LR+ (95% CI)	7.2 (4.9-10.8)	6.1 (4.0-9.1)
LR- (95% CI)	0.81 (0.77-0.83)	0.85 (0.81-0.89)
OR (95% CI)	8.9 (5.7-13.7)	7.1 (4.6-11.1)
Youden's index	0.272	0.148

LR=likelihood ratio; OR=odds ratio

Conclusion

Anti-SmD1 antibodies demonstrate superior utility in the diagnosis of SLE when compared to antibodies targeting the native Sm antigen.

AUTO1-0537
SLE, SJÖGREN'S DISEASE

EVALUATION OF A NOVEL BEAD BASED ASSAY FOR THE DETECTION OF AUTOANTIBODIES TO ANTICELLULAR ANTIGENS IN A LARGE US BASED REFERENCE LABORATORY

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Background

Antibodies to intra-cellular antigens referred to as anticellular (or historically antinuclear antibodies, ANA) are important in the diagnosis of ANA associated rheumatic diseases (AARD). The Avise SLE test is a comprehensive panel for the diagnosis of systemic lupus erythematous (SLE) that utilizes cell bound complement activation products (CB-CAPS) in combination with antinuclear antibodies (ANA). Recently, a novel bead based assay has been developed which allows for the detection of autoantibodies to dsDNA, RNP, Sm, Ro60, Ro52, SS-B, Scl-70, Jo-1, Centromere, DFS70 and Ribo-P. This study aimed to compare the performance of the novel system with reference methods using samples tested in routine.

Method

A total of 2143 samples submitted for Avise SLE testing at Exagen Diagnostics were included in the study and tested in parallel using the methods used in routine (Phadia 250 platform) and using a fully automated bead based assay (research use only, Inova Diagnostics). Qualitative and quantitative correlations were calculated for each of the analytes run on both systems.

Results

The positive (PPA), negative (NPA), total percent agreements (TPA) and kappa values were calculated for each analyte individually using preliminary cutoffs set to yield the best correlation to Phadia. In addition, numerical results were used to calculate the Spearman correlation coefficient. The one Jo-1 positive sample on the Phadia assay, was also positive for the novel bead based assay. All results are summarized in the table below.

Antibody	PPA (95% CI)	NPA (95% CI)	TPA (95% CI)
Sm	92.3% (66.7-98.6)	96.1% (95.1-96.8)	96.0% (95.1-96.8)
RNP	96.7% (83.3-99.4)	88.5% (87.0-89.9)	88.6% (87.2-89.9)
SS-B	90.9% (80.4-96.1)	97.2% (96.4-97.8)	97.1% (96.2-97.7)
Centromere	68.9% (56.4-79.1)	98.4% (97.7-98.8)	97.5% (96.8-98.1)

Conclusion

Our data show good agreement between the results obtained during routine testing and using the novel fully automated bead based immunoassay.

AUTO1-0294
SLE, SJÖGREN'S DISEASE

COULD ELIA CTD SCREEN BE USED AS FIRST LINE TEST FOR THE DIAGNOSIS OF CONNECTIVE TISSUE DISEASE? A SYSTEMATIC REVIEW OF DIAGNOSTIC ACCURACY

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Background

Indirect immunofluorescent (IIF) is considered the most sensitive technique for the diagnosis of CTD. However, IIF is time-consuming, requires skilled operators, has high inter-observer variability and lacks standardization. The fully automated test EliA CTD screen is an alternative to IIF that overcomes these key limitations.

The aim was to assess, using a systematic and unbiased method, whether the fully automated test EliA CTD Screen shows equal diagnostic performance than IIF for CTD.

Method

A systematic review and a qualitative assessment were performed to identify the diagnostic accuracy of EliA CTD screen vs IIF in studies published between 2000 and May 2017.

Methodological quality of included studies was assessed using the QUADAS-2 tool.**Results**

In 12 out of 4814 papers EliA CTD Screen and IIF were directly compared and the diagnostic accuracy was reported. Seven studies reported sensitivity stratified by disease.

Overall Specificity ranged from 78.7% to 96.9% for EliA CTD Screen and from 48.4% to 96.4% for IIF.

Overall Sensitivity ranged from 51.1% to 100% for EliA CTD Screen and from 53.4% to 100% for IIF.

Sensitivity for Lupus ranged from 60% to 91.3% for EliA CTD Screen and from 30% to 100% for IIF.

Sensitivity for Sjögren ranged from 82.4% to 100% for EliA CTD Screen and from 67% to 94.1% for IIF.

Sensitivity for Scleroderma ranged from 58.5% to 100% for EliA CTD Screen and from 69.2% to 100% for IIF.

Conclusion

In this systematic literature review, EliA CTD screen presents higher specificity than IIF. Sensitivity for CTD was disease and method dependent.

AUTO1-0796
SLE, SJÖGREN'S DISEASE

LONGITUDINAL EVALUATION OF TH1(TNF-α, INF-Γ, IL-12) AND TH2 (IL-4, IL-6, IL-10) CYTOKINES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To evaluate, during the period of two years, the sera levels of Th1 cytokines and Th2 in SLE patients and healthy controls, associating these cytokines with disease activity and the different clinical and laboratory manifestations presented by SLE patients, and also, to assess whether cytokines levels and if they could be considered potential biomarkers.
Methods: It was an open, longitudinal study with a control group. Consecutive SLE patients were recruited. Disease activity was determined by [SLE Disease Activity Index (SLEDAI)]. Sera cytokines levels were performed by Enzyme Linked Immunosorbent Assay (ELISA).
Results: Two hundred and eighteen (210 women) SLE patients, with a mean age of 42.62 years [standard deviation (SD) ±11.98 years] 46 (40 women) healthy volunteers with similar age and sex distribution were recruited. IL-6 remained significantly increased in SLE patients compared to healthy controls over time. In the paired analyses, significant fluctuation in IFN-γ ($p=0.026$), IL-12 ($p<0.001$), IL-4 ($p=0.001$) and IL-10 ($p<0.001$) levels were observed. IL-10 levels were associated and correlated with disease activity, at follow up. INF-γ, IL-4 and IL-10 were associated with NP manifestations in SLE patients. There was an association between IL-12 and progressive brain atrophy ($p=0.008$) and a direct correlation between sera IL-12 levels and percentage loss of brain volume ($rs=0.3$; $p=0.015$) was observed.
Conclusion: IL-10 may be considered a biomarker for disease activity and nephritis in SLE. IFN-γ, IL-4 and IL-10 can identify patients with CNS involvement. IL-12 may be considered a biomarker for brain damage in SLE.

AUTO1-0202
SLE, SJÖGREN'S DISEASE

NF-κB2 CONTROLS THE MIGRATORY ACTIVITY OF MEMORY T CELLS TO THE TARGET TISSUES IN A MOUSE MODEL OF SJOGREN'S SYNDROME BY REGULATING EXPRESSION OF CXCR4

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Background

Chemokines and their receptors play a key role in the onset or development of various autoimmune diseases. However, the precise mechanism of T cell migration to target tissues through chemokine/receptor signaling remains unclear. In this study, the contribution of a potent chemokine, CXCL12 and its receptor CXCR4 to autoimmune response of T cells was evaluated using alymphoplasia (*aly*)/*aly* mice, a model of Sjögren's syndrome (SS), which bear a point mutant of nuclear factor (NF)-κB-inducing kinase (NIK) gene.

Method

In vitro migration assay was employed to determine T cell migratory activity. The CXCR4 antagonist AMD3100 was administered into *aly/aly* mice to evaluate the suppressive effect on autoimmune lesions.

Results

In *in vitro* migration assay, migratory activity of effector memory T (TEM) cells to CXCL12 in *aly/aly* mice was significantly enhanced compared with that in *aly/*+ mice.In addition, expression of CXCL12 in target organ of *aly/aly* mice was specifically upregulated in contrast to that in *aly/*+ mice. TEM cells from *RelB*−/− mice but not *NF-κB1*−/− mice also demonstrated greater migratory activity toward CXCL12. The expression of CXCR4 on *aly/aly* TEM cells was increased through transforming growth factor (TGF)β signaling. Finally, administration of a CXCR4 antagonist, AMD3100, suppressed autoimmune lesions in *aly/aly* mice due to reducing the infiltration of TEM cells in target organs.

Conclusion

These results suggest that RelB/NF-κB2 pathway controls migratory function of TEM cells to autoimmune target tissues via CXCL12/CXCR4 axis. Thus, this study will be useful for understanding the pathogenesis of SS and the development of new autoimmunity therapies with manipulating CXCL12/CXCR4.

AUTO1-0118
SLE, SJÖGREN'S DISEASE

Comparison for the response to abatacept for long term efficacy and safety in anti-Ro/SSA-antibody positive 30 patients and antibody negative 76 patients with RA

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Background

Anti-Ro/SSA antibody is the most important autoantibody used as diagnostic markers for Sjögren's syndrome(SS). It was reported that RA patients with secondary SS had worse joint damage than RA without SS. And there is a difference in the clinical results of response to TNF inhibitors and non-TNF inhibitors in anti-Ro/SSA-antibody positive and antibody negative patients with RA. The aim of the study was to compare the response to abatacept for long term efficacy and safety in anti-Ro/SSA-antibody positive patients and antibody negative patients with RA.

Method

We examined 106 patients with RA (30 were positive and 76 were negative for anti-Ro/SSA antibody) who passed after initiation of treatment with abatacept for three years between January 2008 and October 2014. The average level of ACPA,ANA,RF at the initiation time of treatment with abatacept for anti-Ro/SSA antibody-positive patients were higher than that for antibody-negative patients. we compared the clinical characteristics and changes in composite disease activity index, such as DAS28, SDAI, and CDAI, for 3 years in anti-Ro/SSA antibody-positive and antibody-negative patients.

Results

Disease activity was significantly decreased, relative to baseline, in both anti-Ro/SSA antibody-positive and antibody-negative patients by treatment with abatacept. Persistency rate of abatacept for anti-Ro/SSA antibody-positive patients was higher than that for antibody-negative patients

Conclusion

Abatacept is effective in anti-Ro/SSA antibody-positive RA patients as well as other RA patients.

AUTO1-1058
SLE, SJÖGREN'S DISEASE

Q FEVER - A POTENTIAL SLE MIMICKER

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Background

SLE and Q fever can be associated with antiphospholipid antibodies, exhibiting overlapping features and posing a diagnostic challenge.

Method

Report of a case vignette.

Results

A 62-year old male with an ischaemic stroke at the age of 54 and treated with clopidogrel 75mg and rosuvastatin 10mg, presented with a 10-day history of high fevers, asthenia and abdominal pain. Clinically he was febrile (38,8ºC) with a diffusely tender abdomen. Laboratory evaluation showed an inflammatory anaemia, mild leucopenia, prolonged aPTT, mild elevation of transaminases and y-GT, polyclonal hypergammaglobulinaemia, and high CRP (15mg/dL) and ESR (102mm/h). Thoracic and abdominal CT scans revealed polyserositis (pleural and pericardial effusions, and ascites). An extensive work-up for fever of unknown origin found low complement, positive lupus anticoagulant and high titer anti-cardiolipin (IgG and IgM) and anti-β2 glycoprotein 1 (IgG and IgM), with negative ANA, ENA and dsDNA. A diagnosis of SLE with secondary APS was entertained and the patient was switched from clopidogrel to warfarin and started on prednisolone 20mg/day and hydroxicloroquine 200mg/day, with prompt clinical and laboratory improvement. Shortly afterward the pending result from the bone marrow biopsy unveiled the presence of fibrin-ring granulomas. The repeated phase II antibodies for Coxiella burnetii were diagnostic of acute Q fever and the patient completed a 2-week course of doxycycline making a complete recovery.

Conclusion

This case highlights the fact that SLE diagnosis does not rely on a single diagnostic test and can mimic a wide variety of diseases. A thorough approach must be always undertaken in order to avoid diagnostic mistakes.

AUTO1-0523
SLE, SJÖGREN'S DISEASE

THE ANTI-DNA ANTIBODY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic Lupus Erythematosus (SLE) is an autoimmune disease, characterized by production of wide range of autoantibodies. The anti-DNA antibodies was inclused by the ACR and the SLICC as a criterion for SLE. We proposed to study prevalence of anti-DNA antibodies in Tunisien SLE patients and their clinical correlations.

Method

We retrospectively reviewed through a multicentric study 380 patients admitted from 1997 to 2016. All of them fulfilled the 1997 revised ACR criteria of SLE. AAN has been determined by means of indirect immunofluorescence (IIF) and anti-DNA antibodies by means of ELISA.

Results

Anti-DNA antibodies were determined on 88.9% of patients. They were 301 female and 35 male patients. The mean age was 36.8 years. Mean titer of Anti-DNA antibodies was 311 UI/ml [78-258].Systemic manifestations were hematologic (90.8%), rheumatologic (86.3%), dermatologic (79.8%), renal (43.5%) and cardiovascular (34.8%). Study of clinical correlation showed association of anti-DNA antibodies with photosensitivity ($p=0.034$), arthralgia ($p<10^{-3}$), Pulmonary Arterial Hypertension ($p=0.013$), lupus nephritis ($p=0.017$) and cytolysis ($p=0.043$). Anti-DNA antibodies had also association with lupus activity and with drug toxicity relating them to pejorative prognosis.

Conclusion

The anti- DNA antibodies are considered as a specific marker for SLE. It is due to the high frequency [70% to 98%], sensitivity (57.3%), and specificity (97.4%). They are used for monitoring the clinical course especially in the presence of an immunosuppressive treatment. Severallines of evidence demonstrate the pathogenic role of anti-DNA antibodies. In particular, their association with kidney involvement as we found in our study. Many other clinical correlations were found on litérature.

AUTO1-1032
SLE, SJÖGREN'S DISEASE

A COMPARATIVE STUDY OF ANTI-U1RNP, SSA, SSB AND ANTI-NUCLEOSOME ANTIBODIES IN PATIENTS WITH RHEUMATOID ARTHRITIS, SYSTEMIC SCLEROSIS, AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Autoantibody positivity often predicts organ involvement in patients with connective tissue diseases. The aim of our study was to analyze anti-U1-RNP, SSA, SSB and anti-nucleosome autoantibody values in patients with rheumatoid arthritis (RA), systemic sclerosis (SSc) compared to systemic lupus erythematosus patients (SLE), and healthy controls (HC).

Method

We recruited 71 patients with RA, 68 age and sex-matched patients with SLE, SSc and HC. Serum levels of anti-SSA, anti-SSB, anti-U1RNP and anti-nucleosome (chromatin) antibodies were assessed through enzyme-linked immunoassay (ELISA) in all participants. Statistical analysis of the data was done using Microsoft Office Excel and IBM SPSS Statistics v20 for Windows.

Results

Mean values for anti-U1RNP, SSA, SSB and anti-nucleosome antibodies were found to be greater in patients with SLE compared to age and sex-matched patients with RA, SSc and HC ($p<0.001$). Compared to the control group, RA and SSc patients exhibited higher values of anti-U1RNP, SSA, SSB, and anti-nucleosome antibodies ($p<0.05$). Anti-SSA but not SSB antibody levels were significantly greater in RA compared to HC ($p=0.018$). No notable differences in antibody levels were found between RA patients with respect to RF and/or ACPA positivity. Anti-nucleosome as well as anti-SSA antibodies had higher values in SSc patients with diffuse cutaneous involvement compared to the limited form of disease, but results did not reach statistical significance.

Table 1. Differences between age and sex-matched patients with RA, SSc, SLE and HC

	RA (n=71)	SSc (n=68)	SLE (n=68)	HC (n=68)	*p*
AGE (years)	49.07 [21-82]	49.66 [25-81]	48.45 [23-84]	47.32 [25-82]	0.426
U1RNP (U/ml)	36.28 [0-722]	33.62 [0-609]	160.79 [0-867]	14.82 [0-103]	<0.001
SSA (U/ml)	126.54 [0-1746]	69.85 [0-766]	306.61 [0-930]	12.69 [0-51]	<0.001
SSB (U/ml)	37.81 [0-1187]	38.23 [0-938]	164.55 [0-1022]	6.44 [0-55]	<0.001
Nucleosome (U/ml)	22.28 [0-255]	108.11 [0-367]	384.23 [0-2219]	13.70 [0-38]	<0.001

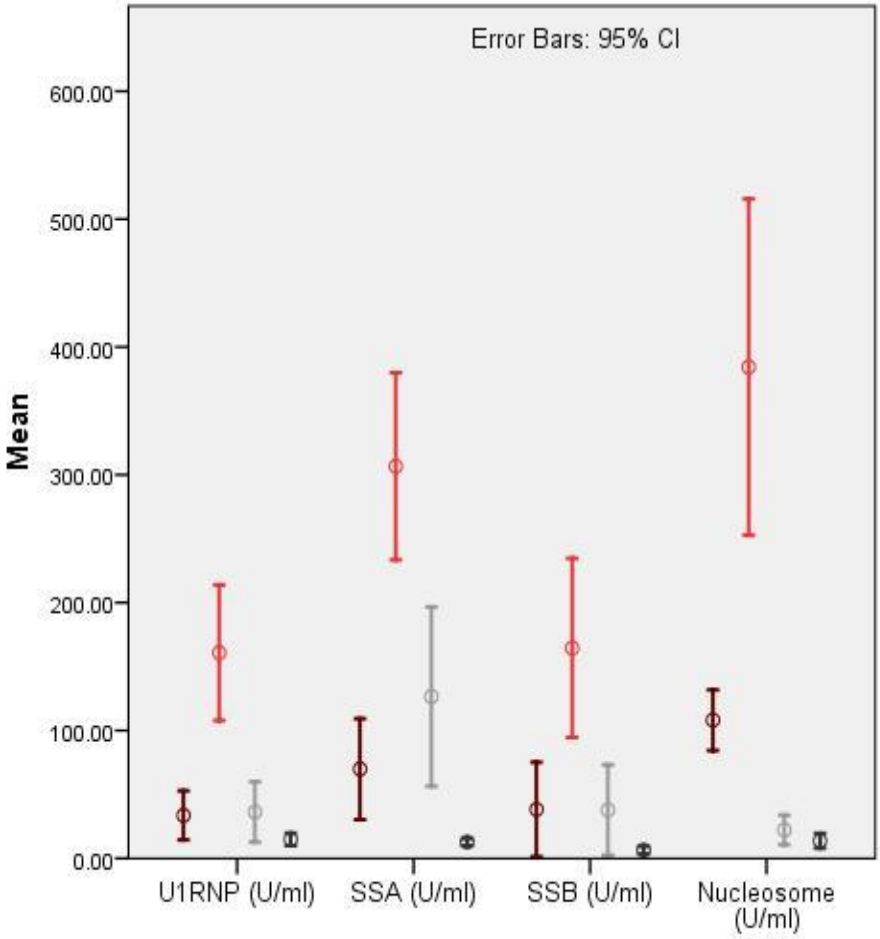

Figure 1. Autoantibody values in patients with SSc, SLE, RA, and HC

Conclusion

Our study found significant differences in anti-U1RNP, SSA, SSB and anti-nucleosome antibody levels in patients with SLE, SSc, RA compared to controls.

AUTO1-1034
SLE, SJÖGREN'S DISEASE

AUTOANTIBODIES DICTATE CLINICAL MANIFESTATIONS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic Lupus Erythematosus (SLE) is known for its multifaceted clinical features and complex immune disturbance. Numerous studies have proven that certain autoantibodies are linked to specific clinical manifestations. However, the diversity of possible associations makes for the uniqueness of each case of SLE. The goal of our study was to analyze the link between clinical presentation and autoantibody titers in Romanian patients with SLE.

Method

We conducted an observational study of 48 adult patients with SLE hospitalized in the Rheumatology Department of the Clinical Rehabilitation Hospital. Venous blood samples were drawn to measure antinuclear antibody levels as well as anti-dsDNA, anti-ssDNA, anti-Sm, anti-U1RNP, anti-SSA, anti-SSB and anti-nucleosome antibody titers (ELISA). Clinical presentation, biochemical tests, SLEDAI score values and urinalysis were extracted from patients' charts. Patient characteristics were included in a database and analyzed using IBM SPSS Statistics v20.

Results

We found statistically significant correlations ($p<0.05$) between cutaneous manifestations and anti-Sm, anti-U1RNP, anti-SSA, anti-SSB and anti-nucleosome antibodies. Kidney involvement correlated with anti-Sm, anti-U1RNP and anti-nucleosome antibodies ($p<0.05$). Joint involvement was strongly associated with the presence of anti-U1RNP antibodies ($p=0.001$). Hematological abnormalities were significantly correlated with anti-dsDNA, anti-U1RNP, anti-SSA and anti-SSB antibodies ($p<0.05$), while ESR and CRP levels were only associated with anti-U1RNP antibodies ($p=0.03$). Furthermore, SLEDAI scores correlated with anti-dsDNA and anti-nucleosome antibody titers ($p<0.05$).

Conclusion

Our data support the relationship between autoantibody titers, disease activity and severity of clinical changes in Romanian patients with systemic lupus erythematosus.

AUTO1-0225
SLE, SJÖGREN'S DISEASE

ANTI-C1Q AND ANTINUCLEOSOME ANTIBODIES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN COLOMBIA

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Background

Anti-C1q and Antinucleosome antibodies have been studied as possible markers of lupus nephritis (LN) and lupus activity with discordant results. Our aim was to evaluate the prevalence of these antibodies in Colombian patients and evaluate the relationship with LN and markers of lupus activity.

Method

A total of 67 patients diagnosed with SLE (ACR 1997 criteria) were included, of which 19 had current LN. Anti-C1q and Antinucleosome antibodies were measured by ELISA (ORGENTEC Diagnostika GmbH). Differences among patients with and without LN and autoantibodies positivity were compared by Mann-Whitney test.

Results

Fifty-one patients were women (87.9%); average age was 33.97 years (SD ± 15.38). Nineteen patients (28.35%) had Anti C1q antibodies (titers on average 23.34 UI/mL, normal up to 10 IU/mL)), 43 patients (64.18%) had Antinucleosome (titers on average 157.63 UI/mL, normal up to 20 IU/mL). In the LN group, the prevalence of positive antibodies was 47.36% for antinucleosome and 26.31% for anti C1q without significant differences among patients with or without LN. The presence of anti-dsDNA antibodies and C4 levels were positively associated with anti-nucleosomes (**Table 1),** whereas proteinuria was negatively associated. Concerning the anti-C1q, these autoantibodies were associated with anti-dsDNA antibodies, and low C3 and C4 levels **(Table 2).**

Table 1. Associations of immunological variables with anti-nucleosomes autoantibodies in patients with SLE.

	Antinucleosome		
	Negative	**Positive**	***p* value**
Anti-DNA* UI/mL	12.5 (10-45.4)	84.8 (10-200)	***0,0025***
C4* mg/dL	18.53 (7-30.55)	10.97 (7.5-17.6)	***0,0146***
Proteinuria* mg/dL	175 (75-484)	20 (20-75)	***0,0193***

Median* (IQR)

Table 2. Associations of immunological variables with anti-C1q autoantibodies in patients with SLE.

	Anti-C1q		
	Negative	**Positive**	***p* value**
Anti DNA* UI/mL	23.05 (10-66.2)	157.75 (47.2-200)	**0,001**
C3* mg/dL	78.8 (60.45-103.5)	50.87 (36.5-66.02)	**0,0007**
C4* mg/dL	14.9 (8.4-22.9)	9.29 (3.01-11.2)	**0,0021**

Median* (IQR)

Conclusion

Antinucleosome antibodies are more prevalent in our population of Latin-American patients comparing to other populations. There was no relationship of anti-C1q and antinucleosomes autoantibodies with LN, although there were associated with anti-dsDNA, and low C3/C4 levels.

AUTO1-0800
SLE, SJÖGREN'S DISEASE

CLINICAL AND IMMUNE CHARACTERIZATION OF PATIENTS WITH PRIMARY SJOGREN'S SYNDROME

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Background

Characterize a cohort of patients with primary Sjogren's syndrome in the Center of Rheumatology in Bogota, Colombia. Primary Sjogren's syndrome is an autoimmune disease that involves the lymphocytic destruction of the salivary and exocrine glands of the affected patients, it can also present a systemic manifestations with multi-organic compromise, consequently its spectrum of presentation is very large.

Method

The samples were processed for ANA and nDNA by Indirect Immunofluorescence assay (IFA) in the automated HELIOS system, then the ELISA tests were performed in the automated SQ2 system. All the results were confirmed with a second specific test. The reagents were from AESKU DIAGNOSTICS.

Results

The clinical characterization included age, diagnostic time, gender, eye symptoms, conjunctival tumor, oral symptoms, xeroderma, and recurrent parotitis.

The prevalence was upper in women than men. The time of evolution of the diagnosis was high, on average 65 months. The main symptom was the ocular manifestations of dry eye, followed by xerostomia the main extra pulmonary sign found was pulmonary involvement, with the presence of isolated bronchiectasis. Only about half of the patients presented clinical arthritis. No patient was found with anti-DNA antibodies positive. Most of the samples were positives for SSA antibodies with fine speckled pattern by ANA.

The prevalence of Anti-Alpha Fodrin IgA antibodies was higher than IgG.

Conclusion

It was possible to make an association between clinical manifestations with serological profiles. In general, the presence of autoantibodies correlates with age of onset, female predominance, increased risk of organ involvement, and the presence of other antibodies.

AUTO1-0763
SLE, SJÖGREN'S DISEASE

EXPRESION OF NUCLEIC ACID BINDING TOLL-LIKE RECEPTORS – IN HEALTHY CONTROL, ANCA ASSOCIATED VASCULITIS AND LUPUS KINDEYS

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Background

Toll-like receptors (TLRs) participate in innate immune response through their ability to recognize and bind to various microbial structures. TLR-7,-8 and -9 are capable of recognizing specific nucleic acids.Systemic lupus erythematosus (SLE) is characterized by a defective monocyte/macrophage-mediated clearance of the apoptotic (nucleic acid-containing) particles in vitro. On the other hand bacterial infections are associated with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV).

Method

The kidney embedded paraffin sections were obtained under informed agreement from 8 patients with lupus nephritis (class II 2 patients, class III 6 patients), 5 patients with AAV with renal involvement and 3 healthy controls without sign of renal disease obtained during autopsy. TLR-7 (LSBio,USA) and TLR-8 and -9 (Sigma-Aldrich,USA) were used for the immunohistochemistry. Proximal and distal tubuli, glomeruli and visceral layers of the Bowman's capsule were scored to 0 (0-5%), 1(6-25%), 2(26-50%) and 3 (>50%) of positive staining for TLRs .

Results

Normal kidney contained some single-stranded RNA binding (TLR-8) receptors but in particular double-stranded RNA binding receptor TLR-7 mostly in distal tubuli and minimal expression of DNA binding TLR-9 was found. SLE kidneys contained more TLR-7, TLR-8 and TLR-9 than healthy controls, however the strongest expression of TLR-8 and -9 was found in tubuli of patients with AAV.

Conclusion

It is concluded that the kidneys have a capacity to bind nucleic acids and that this ability is altered in different types of glomerulonephritides in SLE and AAV.
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AUTO1-0761
SLE, SJÖGREN'S DISEASE

ULTRASOUND PAROTID CHANGES MAY NOT ALWAYS BE RELEVANT FOR LYMPHOMA IN PRIMARY SJOGREN SYNDROME

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Background

Patients with primary Sjogren syndrome (pSS) have a higher lymphoma risk, for which predictor factors were described. Salivary glands ultrasound is a cost-effective method to monitor parotid changes.

Method

We report the case of a female patient with sicca keratoconjunctivitis, diagnosed with pSS at the age of 25, followed up in our unit for 16 years, who developed asymmetric parotid changes.

Results

Upon diagnosis laboratory showed positive anti-Ro and anti-LA antibodies and rheumatoid factor, negative anti-dsDNA, hepatitis serology and cryoglobulins, and normal immunoglobulins and complement fractions. Despite a positive scintigraphy, no ultrasound changes of the salivary glands were initially found. She was treated with symptomatic agents and hydroxychloroquine. As she developed progressive left parotid swelling, we followed her regularly for the risk of developing lymphoma. Ten years from onset, left parotid gland ultrasound showed a large nodular inhomogeneous hypoechoic area, with echogenic stripes, suggesting a Warthin’s tumor. Laboratory showed lymphopenia and inconstantly urinary monoclonal free lambda chains. Although the parotid biopsy did not show malignant transformation, two months later the modified hypoechoic area was surgically removed. Histopathology revealed only lesions typical for pSS. In evolution she developed similar changes on the right parotid gland. Salivary ultrasonography, CT and MRI and hematologic assessment are regularly employed.

Conclusion

Although useful for monitoring, ultrasound findings do not always parallel the histopathology data. A greater index of suspicion is however warranted. Close monitoring and a team approach, including rheumatologist, imagist, maxillofacial surgeon, hematologist and pathologist, are necessary in such cases.

AUTO1-0228
SLE, SJÖGREN'S DISEASE

ANTI-NUCLEOSOME ANTIBODIES IN PATIENTS WITH DISCOID LUPUS ERYTHEMATOSUS

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Background

Discoid lupus erythematosus is an autoimmune disease of the skin without systemic involvement. Autoantibodies studies have been reported in this pathology, establishing that the higher the percentage of autoantibodies positivity, the higher the risk of progression to systemic lupus erythematosus (1). The objective of this study is to evaluate the positivity of autoantibodies in Colombian patients with discoid lupus.

Method

Five patients with diagnosis of discoid lupus erythematosus were included. A complete panel of autoantibodies, including ANAs, Anti- Ro, Anti-La, Anti-RNP, Anti-Sm, Anti-dsDNA, anti-C1q and Antinucleosome, was measured.

Results

All patients were women, the average age was 41 years (SD ± 12.98). Three patients had ANAs (homogeneous pattern at low titers, maximum 1:320). Anti-nucleosome antibodies were found in 2 cases (40%) at high levels (>200 IU/mL, normal up to 20 IU/mL). Anti-dsDNA, Anti-Sm, Anti-Ro, Anti-La and Anti-RNP were all negative. Complement levels were normal in all patients.

Conclusion

The positivity of antinucleosome antibodies in patients with discoid lupus could be a marker of progression to systemic lupus erythematosus and may imply physiopathological pathways in these patients.

AUTO1-1037
SLE, SJÖGREN'S DISEASE

CLINICAL FEATURES OF PATIENTS WITH SYSTEMIC ERYTHEMATOSUS LUPUS IN A DISTRICT HOSPITAL: A RETROSPECTIVE STUDY

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Background

This retrospective study intends to identify the most frequent clinical manifestations of patients with SLE followed in an Autoimmune Diseases Consultation and to analyze the prevalence of the associated cardiovascular risk factors.

Method

The authors analyzed the clinical process of all the patients with the diagnosis of SLE, followed in an Autoimmune Diseases Consultation. The SLICC classification criteria for SLE were used for the definition of “Definitive SLE” and “Presumable SLE”.

Results

The authors identified 50 patients with the diagnosis of SLE, 45 of which were women. The average age at the time of the diagnosis was 48.3 years. The most frequent clinical manifestations were arthralgia (84%), asthenia (42%) and malar rash (30%). 41 patients had at least one analytical evaluation with positivity for ANA and 32 for Anti-dsDNA. 16 patients have been identified as “Presumable SLE”. 37 patients with at least one traditional cardiovascular risk factor were identified, the most frequent of which was arterial hypertension. It was identified cardiovascular disease in 11 patients. None of these patients had antibody antiphospholipid syndrome.

Conclusion

The significative number of patients with “Presumable SLE” is justified by the late appearance of clinical manifestations in many cases, as it is described in literature. Just like other similar studies, it was verified a significative rate of cardiovascular events in this population, although the conclusions are limited by the small sample size. In the future, a bigger prospective study is required, in order to characterize the cardiovascular mortality and morbidity of SLE in a portuguese district hospital.

AUTO1-0735
SLE, SJÖGREN'S DISEASE

HIGH DENSITY LIPOPROTEINS INHIBIT T CELL PROLIFERATION IN SLE

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Background

Systemic lupus erythematosus (SLE) is associated with dyslipidemia and increased cardiovascular risk. HDL is a complex plasma lipoprotein that is recognized for its protective role in atherosclerotic disease. HDL has also anti-inflammatory properties that are not clearly understood. This work aims to show the effect of HDL on T lymphocyte proliferation.

Method

Peripheral blood mononuclear cells (PBMCs) were isolated from 7 SLE patients, with at least 4 SLICC/ACR classification criteria and normal serum lipid profiles, and 3 healthy donors. PBMCs were cultured with and without HDL (at the concentrations of 50, 300 and 600 µg/mL) before CD3 and CD28 stimulation. T cell proliferation was measured by flow cytometry through Ki-67 staining. Regulator T cells (Tregs) phenotyping (CD4+CD25+CD27-FoxP3+) was performed. The expression of the cholesterol transporter ABCA1 in T lymphocytes was also measured by flow cytometry.

Results

HDL decreased T cell proliferation in a dose-dependent manner, with the biggest effect obtained with the physiologic concentration of 600 µg/mL. The inhibition of T cell proliferation was more pronounced in SLE patients than in healthy donors. There were no differences in the prevalence of Tregs between groups. The expression of ABCA1 on the surface of T lymphocytes was also similar between groups.

Conclusion

This study is the first demonstration of a regulatory effect of a lipoprotein, namely HDL, on the adaptive immune system of SLE patients. Here we show that HDL can decrease T cell proliferation even in patients with the disease controlled, which is not correlated with the expression of the ABCA1.

AUTO1-0712
SLE, SJÖGREN'S DISEASE

MALONDIALDEHYDE LEVELS AND INTIMA MEDIA TICKNESS IN SYSTEMIC LUPUS ERYTHEMATOSUS: POSSIBLE ROLE OF UNCOUPLING PROTEIN 2 - 866G/A SNP

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Background

Increased oxidative stress potentially leads to accelerated atherosclerosis and consequently cardiovascular diseases, the main cause of death in Systemic Lupus Erythematous (SLE) patients. To gain insight into these mechanisms, we studied the association of uncoupling protein (UCP)2 genetic variants, a gene involved in the mitochondrial production of reactive oxygen species, and oxidative stress with SLE and the presence of atherosclerosis.

Method

Genetic analysis of the UCP2 -866 G/A and UCP2 Ins/Del polymorphisms was performed in 45 SLE patients and 50 healthy controls by RFLP-PCR. Oxidative status was determined by measuring malondialdehyde (MDA) levels, one of the products of lipid peroxidation. MDA is thought to modify low density lipoprotein particles taken up in monocytes/macrophages hence it could play a role in atherogenesis. Presence of subclinical atherosclerosis was investigated by evaluation of intima-media thickness using echo-colour-Doppler carotid ultrasound examination. Allelic and genotypic frequencies of the SNPs analysed were evaluated by gene count.

Results

Significant association was found between UCP2-866A allele and susceptibility for SLE ($p=0.001$). Higher levels of MDA were found significantly increased in SLE patients (MDA, 5.05±3.36 µmol/L) compared to normal controls (MDA, 2.79±0.89 µmol/L) ($p< 0.0001$).

Conclusion

Our preliminary results suggest that -866G/A UCP2 polymorphism is associated with SLE causing increased ROS levels, that in turn result in increased MDA levels responsible of accelerated atherosclerosis. We believe that our study might offer important information for investigators studying the link between oxidative stress and cardiovascular risk in patients with SLE.

AUTO1-0905
SLE, SJÖGREN'S DISEASE

PREVALENCE OF DEPRESSION AND PERFORMANCE OF FACIT IV QUESTIONNAIRE TO DETERMINE FATIGUE IN SYSTEMIC LUPUS ERYTHEMATOSUS.

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Background

Prevalence of neuropsychiatric symptoms in SLE are among 17 to 71%. Depressive symptoms are around 54%. Fatigue could be due to a conjunction of social factors, pain, sleep and depression and is frequently referred by lupus patients.

To evaluate the prevalence of depressive symptoms and its association with demographics and clinical variables in patients with SLE.

To determine predictive value of FACIT as score for fatigue in a subgroup of depressive SLE vs controls.

Method

Observational, case- control design. SLE patients ≥ 18 ys (ACR 1997), since January to July 2015. We analyzed demographic and clinical variables including SLEDAI (activity scored as ≥4) and SLICC.

Beck II and FACIT (IV version) questionnaires were used for evaluate depression and fatigue respectivelyWe tested two cut points for fatigue by FACIT: < 22 and <40 to determine sensitivity /specificity through this tool in SLE patients vs controls. All the women taken as healthy controls answered both questionnaires described above.**Results**

77 SLE and 100 controls. Prevalence of depression: 52% and 29% (p< 0.05). Prevalence of fatigue (cut point <40): 42% and 36% (p>0.05). FACIT <22 in whole SLE patients: (15%) and FACIT <40: (42%).

FACIT<40 in SLE vs controls: 42% vs 26% (p< 0.05: 69% sensitivity and 84% specificity: 82% PPV, 70% of PNV. AUC to predict fatigue by FACIT in SLE group was 0.75 (0.64-0.87).

Conclusion

Prevalence of depression was high. FACIT IV scale was a good independent predictor of fatigue in SLE with or without depression if a cut off value less than 40 is considered.

AUTO1-0247
SLE, SJÖGREN'S DISEASE

PUTATIVE ROLE OF THE P2X7 RECEPTOR IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

P2X7 is an ionotropic receptor gated by extracellular ATP widely distributed in human tissues with the highest expression in immune cells. P2X7 has important immune-modulatory functions, particularly for its involvement in NLRP3-inflammasome activation and release of IL-1β that, together with other cytokines, i.e. IFN-α, IL-6, could contribute to the pathogenesis of SLE.
The aim of this study was to explore the possible involvement of the P2X7 receptor in the pathogenesis of SLE.

Method

We studied 30 SLE patients, divided into two groups, based on the absence (LN) or presence (LS) of serositis, a condition characterised by raised inflammatory indices, and 15 healthy controls (CS). P2X7 expression and function in peripheral blood mononuclear cells (PBMCs), as well as IL-1 β and IL-6 plasma levels, were analysed.

Results

IL-1β plasma levels in SLE patients were unchanged compared to CS, while IL-6 was increased in the LS group. RT-PCR analysis of PBMCs from SLE subjects showed reduced P2X7 and slightly augmented NLRP3 expression. P2X7 activity, measured as increase of intracellular Ca^{2+} concentration in response to P2X7 agonist, was reduced in PBMCs from SLE patients. Accordingly, *in vitro* IL-1β release by P2X7-stimulated PBMCs was diminished in SLE patients respect to CS.

Conclusion

SLE subjects show altered PBMCs P2X7 expression and function, confirmed by reduced P2X7-stimulated IL-1β *in vitro* secretion. LS patients also present IL-6 involvement, in accordance with the inflammatory condition dictated by serositis. To better define the scenario, other P2X7-dependent responses, such as pyroptosis or T and B lymphocyte functions, should be investigated.

AUTO1-0332
SLE, SJÖGREN'S DISEASE

RISK FACTORS FOR PULMONARY INVOLVEMENT IN PRIMARY SJÖGREN'S SYNDROME: RESULTS OF A PROSPECTIVE REGISTRY STUDY

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Background

Pulmonary involvement in Primary Sjögren's syndrome (pSS) is associated with increased mortality, thus the study of the risk factors associated with this involvement is important. Objective: To evaluate the risk factors associated with the pulmonary involvement in pSS.

Method

We evaluated 131 pSS patients included from june/2016 to june/2017 in a prospective registry study approved by the local Ethics Committee. All patients met the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) 2016 classification criteria for SSp. Disease activity was assessed at inclusion according to the EULAR SS Disease Activity Index-ESSDAI. Extraglandular manifestations were defined according to the ESSDAI.

Results

Thirty-eight of 131 pSS patients (29%) had pulmonary involvement (lymphocytic interstitial pneumonitis- 48.1%, non-specific interstitial pneumonitis- 37% and usual interstitial pneumonitis- 14%). Patients were divided into two groups: with/without pulmonary involvement. These groups were comparable on age (57.1±13.8 vs. 53.1±13.1 years, p=0.127), race (white: 67.6 vs. 83.1%, p=0.060), gender (female: 94.7 vs. 93.5%, p=1.000) and time of diagnosis (10±7.2 vs. 8.8±6.5 years, p=0.345), respectively. Frequencies of sicca symptoms and extraglandular involvements were comparable in the two groups: arthritis (50 vs. 33.3%), vasculitis (13.2 vs. 17.20%), peripheral neuropathy (5.3 vs. 6.5%), multiple sclerosis-like disease (0 vs. 2.2%), renal tubular acidosis (10.5 vs. 9.7%) and haematological (34.2 vs. 29.03%), respectively (p>=0.113). In contrast, Rheumatoid Factor (RF) [81.6 vs. 62.9% (p=0.040)] and higher ESSDAI values [7.0±4.1 vs. 2.5±3.07, p=0.0001] were associated with pulmonary involvement.

Conclusion

The main risk factors associated with pulmonary involvement in pSS were RF and ESSDAI.

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AUTO1-0936
SLE, SJÖGREN'S DISEASE

EVALUATION OF FIVE NON-RADIOACTIVE-IMMUNOASSAYS FOR THE DETECTION OF ANTI-DSDNA AUTO-ANTIBODIES IN THE FOLLOW-UP OF LUPUS FLARES.

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Background

Early diagnostic of renal impairment in systemic lupus erythematous (SLE) combined by a strict follow-up of patients are important to avoid morbidity and mortality. Serum level of anti-dsDNA antibodies is commonly used to monitor flares in SLE patients. Farr assay remains the gold-standard for anti-dsDNA quantitative detection, however new quantitative non-radioactive-immunoassays (NRIA) could be a good alternative to the radioactive-immunoassay.

Method

The aim of this study was to analyse the accuracy of five commercial NRIA to detect flares on samples pre-characterized by Farr assay (TrinityBiotech). Seventeen flares from fourteen patients were included. Each serum was analyzed by ELISA Anti-dsDNA-NcX® (EUROIMMUN), ELISA QUANTA Lite® HA dsDNA (Inova Diagnostics), FEIA EliA dsDNA® (ThermoFisherScientific), CLIA QUANTA Flash® dsDNA (Inova Diagnostics) and CLIA Zenit RA dsDNA® (Menarini). A control group of 20 rheumatoid arthritis patients was used.

Results

All NRIA detected 16/17 flares without significant differences in kinetic values. One flare showed similar results with four tests but for Anti-dsDNA-NcX® (EUROIMMUN) assay, the values don't correlate with the symptomatology of the patient. Specificity of the five assays varies from 95 to 100%. The inter-run CV was higher with ELISA methods (the Anti-dsDNA-NcX® (EUROIMMUN) ELISA was incubated manually), compared with others (mean of CV values of 18% for ELISA, versus 7% for CLIA and 6% for FEIA respectively).

Conclusion

All the non-radioactive tested assays seem to be a good alternative to the radioactive-immunoassay for the follow-up of lupus flares. However these results should be confirmed with further study on a large population of patients.

AUTO1-0698
SLE, SJÖGREN'S DISEASE

PREVALENCE OF HYPOVITAMINOSIS D IN 70 PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOUS AND THE RELATIONSHIP WITH SLEDAI-2K IN PATIENTS TREATED IN TWO RHEUMATOLOGY SERVICES, BOGOTA 2017.

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Background

Vitamin D is a steroid hormone with pleiotropic effects on physiological processes. This one works on immune system and low level was associated with SLE.*1. A research in a colombian clinic found a prevalence of hipovitaminosis D of 87% in healthy population, but hypovitaminosis D is higher in SLE patients than healthy controls. *2.
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Method

To establish the prevalence of hypovitaminosis D in 70 patients with SLE and relationship with SLEDAI – 2K.Methods. A cross sectional study was carried out. Medical records with a diagnoses of SLE o CIE-10 M30-M36 were identified and we included patients >18 years of age who meet at least 4 of the 11 criteria to diagnoses of SLE for medical record. The analysis included means, DS and Kruskall Wallis with p-value < 0.05

Results

The 94% of patients are women, with an average age of 39.9 years, married (41%), with secondary education (56.7%) . It was found that the patients with higher activity, had lower vitamin D levels and patients with lupus nephritis even more.

Conclusion

The results show that patients with SLE with severe activity by SLEDAI-2K have lower levels of vitamin D levels and the kidney involvement was associated with the lowest levels of vitamin D .

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AUTO1-0922
SLE, SJÖGREN'S DISEASE

ASSOCIATION OF IL-4 WITH DISEASE ACTIVITY, ACTIVITY INDEX , AND CHRONICITY INDEX IN LUPUS NEPHRITIS

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Background

To study the association of IL-4 serum level in with Lupus Nephritis (LN) disease activity , Activity and Chronicity Indices of LN in Saiful Anwar Hospital

Method

Subjects were 37 patients with LN (ACR 1997 revised criteria for SLE with lupus nephritis WHO class III and IV) . IL-4 serum level was measured using ELISA . LN Disease Activity was assessed using renal domain SLEDAI scores (mild disease activity : score ≤ 4). Activity Index (low activity : activity index < 6) and Chronicity Index of LN (low chronicity : chronicity index < 3) were scored using the NIH system.

Results

LN patients with mild disease activity (24 patients) had significantly higher serum level of IL-4 compared with LN with high disease activity (13 patients) (133.17 + 79.93 pg/mL vs. 86.33 + 70.62 pg/ml, p=0.039). IL-4 serum levels in LN patients with the low activity index (29 patients) was not significantly different compared[HK1] to LN patients with high activity index (8 patients) (144.49 + 81.79 pg/mL vs. 124.77 + 73.01, p:0.599). Serum level of IL-4 was significantly higher in the LN patients with high chronicity index (21 patients) compared to LN patients with low chronicity index(16 patients) (147.61 + 87.20 pg/mL : 76.16 + 42.32 pg/mL, with p=0.012).

Conclusion

IL-4 may have an important role in the fibrogenesis in patient with LN (with high chronicity index) .

AUTO1-0338
SLE, SJÖGREN'S DISEASE

FREQUENCY AND PATTERNS OF PRESENTATION OF SJOGREN SYNDROME AMONG SUDANESE PATIENTS PATIENTS ATTENDING THE RHEUMATOLOGY CLINICS IN KHARTOUM STATE DURING 2016

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Background

Sjögren's syndrome is a chronic systemic autoimmune disease characterized by lymphocytic infiltriation of exocrine glands. Sjögren's syndrome has a strong female propensity with the mean age of onset in the 4th to 5th decade. Clinical presentation varies from mild symptoms, such as kerato-conjunctivitissicca, and xerostomia, to severe systemic symptoms involving multiple organ systems. There are a limited number of studies that have been published on the epidemiology of Sjögren's syndrome.Aims of this study is to calculate the frequency and percentage of Sjögren's syndrome cases among the outpatients rheumatology clinics in three public hospitals, during (November2015 till may 2016)

Method

- This descriptive cross-sectional hospital based study conducted in the outpatient rheumatology clinics in the three hospitals, total coverage done and used questionnaires used as a tool for data collection. Then analysis done through statistic programme for social science version 21 and represented the figures and tables by Microsoft Office 2010.

Results

From 2640 patients with different rheumatologic diseases , eighty patints diagnosed with Sjögren's syndrome were selected ,which is equal to (3.03%).Seventeen out of 2640 (0.49%) were found to be pure (primary) Sjögren's and the other sixty three cases (2.38%) were diagnosed as Sjögren's syndrome associated with other autoimmune diseases. The majority of the patients were female 69 cases while male were 11.

Conclusion

:- Sjögren's syndrome is common in female with range age of (40-60) years with a mean of 48 years. The frequency of Sjögren's syndrome patients to other rheumatologic diseases range from (2.8%) to (4.2%)

AUTO1-0788
SLE, SJÖGREN'S DISEASE

AUTOFAGIA IN Treg CELLS AND PROLACTIN RECEPTORS IN B LYMPHOCYTES OF PATIENTS WITH ACTIVE LUPUS NEPHRITIS

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Background

Systemic Lupus Erythematosus (SLE) is characterized by over-production of autoantibodies. Alterations in autophagy, apoptosis, T, B lymphocytes and prolactin contribute to these alterations.
OBJECTIVE: To analyze the relationship between autophagy in Treg lymphocytes and expression of prolactin receptors (PRL-R) in B lymphocytes of SLE patients.

Method

We included patients diagnosed with SLE and healthy individuals. The activity of SLE was determined by SLEDAI. In blood sample we analize Treg lymphocytes, CD25 + FOXP3 + and B lymphocytes, CD19 +. Autophagy was identified with the anti-ATG14 antibody and PRL-R using the anti-PRL-R. The labeled cells were identified by flow cytometry. The results were analyzed by T of student's and Anova.

Results

We included 40 patients with SLE, 20 active, 20 in remission and 20 healthy controls. Our results are:

1.Autophagy (%) in Treg cells: Healthy control vs. Inactive SLE: 7.44 vs 8.74 p= >0.9999. Healthy control vs. Active SLE: 7.44 vs 12.11 p= <0.05
2. Autophagy (%) in lupus glomerulonephritis: Healthy control vs. Active SLE: 7.44 vs.13.63 p= 0.0003. Healthy control vs. Inactive SLE: 7.44 vs. 9.9 p= 0.1178
3. Prolactin Receptor in B lymphocytes:Healthy Controls vs Inactive SLE: 0.62 vs 3.56 p= 0.7463. Heatlhy Controls vs Active SLE: 0.62 vs 50.79 p= <0.0001.
4. Prolactin Receptors in lupus glomerulonephritis: Healthy Controls vs Inactive SLE: 0.62 vs 51.22 p= 0.0001. Heatlhy Controls vs Active SLE: 0.62 vs 4.53 p= 0.0022

Conclusion

The increase of autophagy in Treg and PRL-R in B lymphocytes participate in active lupus glomerulonephritis. Autophagy and PRL-R may be new therapeutic targets in SLE.

AUTO1-0209
SLE, SJÖGREN'S DISEASE

CLINICAL RELEVANCE OF ISOLATED ANTI-U1 SMALL NUCLEAR RIBONUCLEOPROTEIN A (snRNP-A) AUTO-ANTIBODIES

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Background

Anti- U1 small nuclear ribonucleoprotein (snRNP) autoantibodies are directed against snRNP-70 kDa, snRNP-A (32 kDa) and snRNP-C (22 kDa). Anti-snRNP-A auto-antibodies have been considered to be a predictive markers of systemic lupus erythematosus (SLE) and can appear three years prior the diagnosis.

Aim: to determine the clinical utility of the detection of the anti-snRNP-A antibodies in routine practice using the automated multiplex platform-BioPlex® 2200.

Method

10150 sera were analysed by BioPlex according to the manufacturer instructions. 231 (2.3%) had isolated anti-snRNP-A (index >1). 16% of the positive sera (36/231) had a high level of anti-snRNP-A antibodies (index >5). All other antinuclear antibodies were negative.

The immunofluorescence pattern on HEp2 cells was: negative (49%), homogeneous (22%), homogeneous and speckled (16%), speckled (10%) or nucleolar (3%).

Clinical data were obtained for these 231 patients.

Results

33% (77/231) of isolated anti-snRNP-A are detected in sera of patient suffering from autoimmune diseases: rheumatoid arthritis: 17, systemic lupus erythematosus: 13, systemic sclerosis: 9, inflammatory bowel disease: 10, autoimmune thyroiditis: 5, autoimmune hepatitis: 5, other autoimmune diseases: 18.

67% (154/231) are detected in sera of patient with no autoimmune disease: arthritis: 27, lung disease: 22, nephropathy: 16, carcinoma: 15, neuropathy: 13, infectious disease: 10, vascular injury: 9, heart disease: 6, hematologic disease: 5, other: 31.

36 patients had a high level of anti-snRNP-A (index >5), 12 (33%) suffered from autoimmune diseases.

Conclusion

In our study, the positivity of isolated anti-snRNP-A antibodies is not specific for autoimmune disease, whatever the level of antibodies may be.

AUTO1-0787
SLE, SJÖGREN'S DISEASE

ANALYSIS OF CD28 HAPLOTYPES IN MEXICAN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME FROM THE WESTERN OF MEXICO: ASSOCIATION WITH THE SOLUBLE LEVELS

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Background

Primary Sjögren's syndrome is an autoimmune disease characterized by a T and B cells infiltrate in exocrine glands causing destruction or hypofunction of themselves. CD28 is a coestimulator of T cells necessary for its correct activation and function. The *CD28* -372 G>A and IVS3+17 T>C polymorphisms could alter CD28 expression leading to a lengthy response and therefore to a higher clinical severity in this disease.

Method

136 patients with pSS and 138 healthy subjects (HS) from western of Mexico were included. Genotyping was performed by PCR/RFLP technique and sCD28 quantification was realized by ELISA commercial kit.

Results

Polymorphisms were in Hardy-Weinberg equilibrium. *CD28* -372 G>A polymorphism was not shown difference between pSS and HS. IVS3+17 T>C polymorphism was shown a difference in both C allele (pSS 17% *vs* HS 24%, p=0.0161; OR=0.603[CI95%:0.399-0.913]) and CC genotype (pSS 1% *vs* HS 7%, p=0.0114; OR=0.191[CI95%:0.041-0.889]). GC *CD28* haplotype was associated with protection to develop pSS (pSS 13.2% *vs* HS 22%, p=0.0071; OR=0.543 [CI95%:0.346-0.851]). sCD28 levels was not shown difference in both groups. Higher levels were observed in HS who carrier GC haplotype (pSS:0.86 *vs* HS:2.1ng/mL).

Conclusion

GC *CD28* haplotype was associated with protection to develop pSS which is evidenced for higher levels of sCD28 in HS. This results needs to be corroborated in other cohorts of the country.

AUTO1-0807
SLE, SJÖGREN'S DISEASE

THE COMPARISON OF SERUM CONCENTRATIONS OF IgG4, TOTAL IgG, C4,C3 COMPLEMENT COMPONENTS IN PATIENTS WITH SJÖGREN'S SYNDROME, SUBJECTS WITH DRYNESS SYMPTOMS AND HEALTHY INDIVIDUALS.

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Background

Immunoglobulins G are particularly important for the secondary immune response, IgG4 subclass is least numerous and currently draws special attention as the group of IgG4 related diseases has been distinguished.

Method

pSS group: 48 individuals [mean age 51]; 83%F/17%M; sicca group(S)20 subjects with the symptoms of dryness[mean age 58] 85%F/15% M; control group 20 healthy subjects [mean age43]100%F. Serum concentrations of IgG4, IgG, C4,C3 complement components were measured by nephelometry. Ethics Committee of NIGRiR approved. Statistics:U Mann-Whitney test (continuous variables),Spearman correlation coefficient(correlations quantative variables). Statistical significance-$p<0.05$.

Results

There were no significant differences in the tIgG and IgG4 between pSS and Sgroup. In both a reduction of IgG4 was observed,greater in pSS group. pSS patients had significantly lower IgG4 compared to control group ($p<0,0435$). There was no such evident correlation between S and control group. The concentration of tIgG,and tIgG/IgG4 ratio was significantly lower in the pSSgroup compared to the control group($p<0,0245$; $p< 0.0035$ respectively). In pSSgroup the C4 was significantly lower compared to Sgroup and healthy controls($p<0,05$). Weak negative correlation was between C4 and IgG4($r= - 0,274$)in all groups.

Conclusion

Decreased level of IgG4 in patients with pSS compared to healthy subjects, may be linked to the type of polyclonal B-cell activation present in pSS and results from the lower C4 concentrations and lack of stimulation for IgG4 production (despite hypergammaglobulinaemia) both existing in pSS. No significant differences in the IgG4 between pSS and S groups may result from the effect of EBV infection (previous/ reactivation), which prevails in both groups(data not shown).

AUTO1-0809
SLE, SJÖGREN'S DISEASE

COEXISTENCE OF SYSTEMIC LUPUS ERYTHEMATOSUS AND DEVIC'S DISEASE

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Background

Coexistence of Systemic Lupus Erythematosus (SLE) and Devic's Disease (DD) is extremely rare, with an incidence of 1 in 5,000,000.

Objective: To describe the evolution of 4 SLE cases associated with DD.**Method**

We reviewed 4 cases with coexistence of SLE (ACR criteria) and DD (NMSS 2010 criteria). Descriptive statistics was used.

Results

Case A: A 55 year-old female diagnosed with SLE 21 years ago, presented optic neuritis, multiple mononeuritis and myelitis. DD diagnosed 7 years ago with transverse myelitis, 8 relapses, anti-aquaporin-4 antibodies (IgGNMO)+. Initial EDSS: 6, current: 6. Treatment: Rituximab because of lack of response to previous treatment.

Case B: A 75 year-old female, started with left optic and retrobulbar neuritis 11 years ago. SLE diagnosis 9 years ago, presented incomplete medullar syndrome T3-T4. DD diagnosed in 2015 with IgGNMO+. Initial EDSS:3,current: 7. Treatment: 5 plasmapheresis sessions, currently on Rituximab.

Case C: A 54 year-old female, mucocutaneous SLE for 34 years, later optic neuritis with 5 relapses, IgGNMO+ and myelitis. Initial EDSS:7,current:7. Treatment: 5 sessions of plasmapheresis, currently on Rituximab.

Case D: A 32 year-old female, optic neuritis and bilateral amaurosis, SLE diagnosis. Complete medullary syndrome in T8, and diagnosis of DD 4 years ago. Initial EDSS: 3, current: 3. Treatment: 5 sessions of plasmapheresis, currently on Rituximab. All previous cases currently with inactive SLE.

Conclusion

The association of SLE and DD is exceedingly rare.These patients had severe clinical manifestations with a higher number of relapses and permanent sequelae being diagnosis and treatment of these conditions a medical challenge.

AUTO1-0331
SLE, SJÖGREN'S DISEASE

CD4+CD25+FOXP3+ REGULATORY T CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: THE NEGATIVE ASSOCIATION WITH DISEASE ACTIVITY, ACUTE COURSE, TRANSITIONAL B CELLS AND IGG LEVELS

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Background

CD4+ CD25+ Foxp3+ regulatory T (Treg) cells play a key role in maintaining peripheral tolerance and preventing autoimmune disease. Quantitative and/or qualitative deficiencies of Treg have been associated with immune disturbances in systemic lupus erythematosus (SLE). The main goal of the study was to determine the relationship of CD4+CD25+FoxP3+Treg cells with clinical and immunological manifestations in SLE patients (pts).

Method

Frequencies and absolute numbers of peripheral blood CD4+CD25+FoxP3+Treg cells were assessed in 21 healthy donors and 20 SLE pts (2012 SLICC classification criteria); (1M/19F); age 32±13 years; disease duration median (25–75 percentile) 5(1-10) years; SLEDAI2K≥10 - 15(10-22) (14 pts), <10 – 7(6-8) (6 pts). All pts were treated with prednisone, hydroxychloroquine, azathioprine, mycophenolate mofetil, cyclophosphamide. CD4+CD25+FoxP3+ Treg cells and B-cell subsets were analyzed using multicolor flow cytometry.

Results

Compared with healthy donors, SLE pts demonstrated significant lower the absolute number of Tregs (0.05; 0.04-0.06 vs 0.03;0.02-0.05x10^9/L, p<0,036), with a high percentage Treg (8.8;7.5-10.5 vs 12.0;8.8-17.0%, p<0.02). The median percentage of Tregs was lower in pts with acute SLE compared to chronic SLE pts (9.0;8.3-9.9 vs 13.5;12.7-18.7%, p<0,02). SLE pts with high activity had a lower frequencies of Tregs (10.2;8.5-15.0 vs 15.8;12.7-20.4%, r=-0,51, p<0,05). Low count of Tregs correlated with elevated level of IgG (r=-0,52, p<0,05). Absolute number of Tregs correlated negatively with percentage and absolute count of transitional (CD19+IgD+CD10+CD38++CD27-) B cells (r=-0,66 and r=-0,63, p<0,05).

Conclusion

Decreased amount of T regs in SLE is associated with high disease activity, acute course and expansion of autoreactive B cells.

AUTO1-0534
SLE, SJÖGREN'S DISEASE

DIAGNOSTIC ACCURACY OF OBJECTIVE ITEMS FOR PRIMARY SJOGREN' S SYNDROME

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Background

Objective: To test diagnostic accuracy of ocular and oral symptoms, sialoscintigraphy, anti-SSA antibody and focus score (FS) for primary Sjogren's syndrome, compared to biopsy of minor salivary gland (MSG) as gold standard.

Method

Total 190 subjects were evaluated for the diagnosis of pSS. All subjects underwent a diagnostic evaluation for pSS: questionnaire wih six questions to assess ocular and oral symptoms; presence of anti-SSA antibodies; sialoscintigraphy and biopsy of MSGs with determination focus score (FS). Statistical analysis was performed by SPSS version 19. The area under the receiver operating characteristiscs curve (AUC-ROC) was used to evaluate the diagnostic accuracy of each diagnostic items.

Results

Out of 190 subjects examined, 140 subjects (mean age 54.5 years) fulfilled the American-European Criteria for pSS, whereas 50 subjects (mean age 52.6 years) were classified as non-pSS subjects. The frequency of ocular and oral symptoms were significantly higher in the pSS group ($p=0.042$ and $p=0.054$, respectively). The difference between the pSS and the non-pSS was statistically significant for positive sialoscintigraphy ($p<0.001$), anti SS-A antibody ($p<0.001$), as well as for positive FS ($p<0.001$). The diagnostic accuracy for ocular and oral dryness was poor [AUC-ROC 0,67±0,04, AUC-ROC 0,63±0,04, respectively]. The diagnostic accuracy anti-SSA antibody and sSC was similare [AUC-ROC 0,74±0,39, AUC-ROC 0,78 ± 0,03, respectively], while diagnostic accuracy of FS was best [AUC 0,88±0,02].

Conclusion

High diagnostic accuracy of anti-SSA antibody, sialoscintigraphy and focus score confirmed their value for determination pSS. Symptoms of dryness were not specific and important for diagnosis pSS.

AUTO1-0631
SLE, SJÖGREN'S DISEASE

APOPTOTIC BODIES CONTAINING dsDNA COVALENTLY MODIFIED BY PARVOVIRUS B19 NON-STRUCTURAL PROTEIN NS1 INDUCE dsDNA AUTOANTIBODIES AND END ORGAN DAMAGE IN NON-AUTOIMMUNE MICE

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Background

Persistent viral infections can induce aberrant immune responses and are implicated in the development of autoimmunity. Parvovirus B19 (B19V) non-structural protein, NS1, a helicase, covalently modifies self dsDNA and induces apoptosis. This study was undertaken to determine whether resulting apoptotic bodies (ApoBods) containing virally modified dsDNA could induce autoimmunity in an animal model.

Method

Non-autoimmune BALB/c mice were inoculated with B19V NS1, pristane or staurosporine induced ApoBods. At 1, 4, and 8 weeks post-inoculation, serum was tested for dsDNA autoantibodies by *Crithidia luciliae* staining and ELISA. Brain, heart, liver and kidney pathology was examined by bright field and confocal microscopies at 8 weeks. Deposition of self-antigens and ApoBods in glomeruli was examined by staining with labeling antibodies to dsDNA, histones H1 and H4, and TATA-binding protein.

Results

Inoculation with B19V NS1-induced ApoBods induced dsDNA autoantibodies in a dose dependent fashion, whereas staurosporine induced ApoBods did not. Histopathological features of immune mediated organ damage were evident in pristane-induced and B19V NS1-induced ApoBod groups and severity scores were significantly higher in these groups than in staurosporine treated groups, and was B19V NS1-induced ApoBod dose dependent. Nucleosomal antigens were deposited in pristane-induced and B19V NS1-induced ApoBod groups, but not in the staurosporine-induced ApoBod group.

Conclusion

This study demonstrated proof of principle in an animal model that virally modified dsDNA in apoptotic bodies could break tolerance to self dsDNA and induce dsDNA autoantibodies and end-organ damage. The study helps explain observations suggesting a viral contribution to the development of systemic lupus erythematosus.

AUTO1-0790
SLE, SJÖGREN'S DISEASE

COMPARATIVE STUDY OF TWO METHODS OF ANTI-dsDNA ANTIBODIES DETECTION: ELIA PHADIA 250 VERSUS CRITHIDIA LUCILIAE IMMUNOFLUORESCENCE TEST (CLIFT)

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Background

The anti-dsDNA antibodies detection is one of the major biological criteria in systemic erythematosus lupus (SLE). Sensitivity and specificity may differ widely according to the assay in use.

The purpose of the study is to compare two anti-dsDNA antibodies detection assays: a sensitive automatized fluorescent immunoassay (Phadia, EliA), versus a specific assay: Crithidia luciliae immunofluorescence test (CLIFT).

Method

The prospective study included 277 samples which were tested for anti-dsDNA antibodies with both assays (Phadia EliA and in house CLIFT based assay).

The positivity threshold by CLIFT method corresponds to a title equal or higher than 1/10 and a concentration of 15UI/mL by EliA. A FARR test was carried out for discordant results.

Results

Out of 277 samples, 68% were double negatives and 13% were double positives with both methods. This means that in total, 81% of the results were concordant.

The SLE diagnosis was confirmed in 34 out of 36 double positive patients (94%).

Discordant results showed 7 isolated positives in EliA (non-confirmed in CLIFT), including only 3 SLE patients.

Surprisingly, CLIFT brought 27 positive results, discording with EliA. Among those were 13 active SLE, 5 SLE induced by anti-TNF treatment, 2 connectivities, 1 angio immunoblastic lymphoma, and 6 without any obvious auto-immune pathologies, two of which had a negative FARR test.

Conclusion

We found a relatively global concordance between the two techniques: EliA and CLIFT.

CLIFT assay demonstrated better analytical performances in SLE suspected patients screening, despite technical draw-back (time-consuming and need for trained personnel).

AUTO1-0358
SLE, SJÖGREN'S DISEASE

ANALYSIS OF FOLLICULAR HELPER T CELLS IN A MOUSE MODEL FOR SJOGREN'S SYNDROME

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Background

Follicular helper T (Tfh) cells play a key role in the pathogenesis of various autoimmune diseases. Tfh cells contribute to the formation and maintenance of germinal center (GC) in the lymphoid tissues or inflammatory lesions. Sjögren's syndrome (SS) is an autoimmune disorder that affects salivary and lacrimal glands. The precise mechanism of the onset of autoimmune lesions and autoantibody production in SS though Tfh cells remains unclear. In this study, we evaluated how Tfh cells contribute to the pathogenesis of SS using a mouse model.

Method

We evaluated a mouse model for SS, NFS/*sld* mutant mice thymectomized at 3 days after birth. We examined the proportion of Tfh cells and GC B cells in cervical lymph nodes (cLN) and spleen (Sp) of SS model.

Results

The proportion of Tfh cells and GC B cells in cLN and Sp of SS model mice was significantly increased compared with that of control mice, together with increased serum autoantibody levels. In addition, more enhanced GC formation in SS model was found by immunofluorescence analysis. Furthermore, *in vitro* induction of Tfh cell differentiation using naïve $CD4^+$ T cells from SS model was promoted. B cell depletion therapy with anti-CD20 antibody *in vivo* resulted in a decrease in Tfh cells and GC B cells, and suppression of autoimmune lesions independent on autoantibody production.

Conclusion

These results imply that Tfh cells and GC B cells play an important role in the formation of autoimmune lesions in the target organ of SS.

AUTO1-1001
SLE, SJÖGREN'S DISEASE

TRANSVERSE MYELITIS AS INITIAL MANIFESTATIONS OF SJOGREN SYNDROME

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Background

Sjogren syndrome (SS) is an autoimmune disorder characterized mainly by decreased exocrine gland function. The condition typically develops gradually beginning in middle adulthood, but it can occur at any age.

Method

A 82-year-old woman, presented with four-month history of back pain, followed by weakness and numbness of the legs, with deficit motor skills and dysfunctional urethral activity. When asked, she revealed xerostomia and xerosis. Neurologic examination revealed asymmetric paraparesis in legs. Spinal cord MRI showed lesions in the cervical spinal cord with medullar compression in C4-C5, hyper intense lesion involving long segment from T2 to conus medullaris, with contrast-enhancing in some areas, confirming the diagnosis of transverse myelitis. Her investigations showed positive ANA, anti-SSA and anti-SSB antibodies and presence of focal lymphocytic sialadenitis with a focus score >1 in salivary gland biopsy. These findings are consistent with the diagnostic criteria for SS.

Results

We treated her with azathioprine 2 mg/kg/day and prednisone 1 mg/kg/day. After two months of treatment, she could walk with assistance but still with urethral sphincter dysfunction.

Conclusion

Although in most people with SS xerostomia and xerosis are the primary features of the disorder, patients with SS may have involvement of many types of organs beyond the exocrine glands.

AUTO1-0211
SLE, SJÖGREN'S DISEASE

THE PREDICTIVE VALUE OF B CELL NUMBER REDUCTION IN A COHORT OF PATIENTS WITH REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH BELIMUMAB

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Background

Belimumab, the anti-B-cell activation factor (BAFF) agent, is approved for the treatment of refractory systemic lupus erythematosus (SLE). Its effect on the number of circulating B-cells is selective on naïve (CD19+CD27-IgD+) and immature transitional B-cells (CD19+38high24high) whose survival is strictly BAFF-dependent. On the opposite, CD27+ memory B-cells are preserved during belimumab therapy, being their maturation more related to the activation of B-cell receptor pathways. The aim of this study is the evaluation of B-cell subpopulations in a cohort of SLE patients treated with belimumab.

Method

Phenotypic analysis of peripheral blood B-lymphocytes was made by flow-cytometry in 10 SLE patients treated with belimumab. SLE-disease activity was assessed by SLEDAI-2K score. BAFF was tested by ELISA. SPSS was used for statistical analysis.

Results

The relative change of BAFF levels at 6 and 12 months from baseline showed linear correlation with the percentage of naïve B-cells (Pearson correlation=0.645, p=0.044 and 0.639, p=0.002, respectively) and of transitional B-cells (Pearson correlation=0.768, p=0.009 and 0.623, p=0.055, respectively). The percentage and absolute number of naïve B-cells showed a progressive decrease during time (ANOVA, p=0.013 and p=0.001 respectively). In terms of response prediction, a significant association of SLEDAI percentage improvement at 12 months with the decrease of total number of B-cells within the first 6 months of therapy was observed (Log regression r=0.707, p=0.05).

Conclusion

BAFF inhibition induces B-cell number modifications in a SLE cohort. The reduction of total number of B-cells within the first six months shows predictive value for SLEDAI response after the first year of therapy.

AUTO1-0559
SLE, SJÖGREN'S DISEASE

LUPUS IN CHILDHOOD AND ADOLESCENCE: A CASE REPORT

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Background

Systemic lupus erythematosus (SLE) is an autoimmune multisystem chronic inflammatory disease. The diagnosis of systemic lupus erythematosus (SLE) in children is challenging. The heterogeneous manifestations and disease impact on the child's growth highlight the importance of timely diagnosis and management.

Approximately 15–20% of all SLE cases are diagnosed in childhood. Childhood SLE affects girls more often than boys (8:1), even in the prepubescent age group (4:1). SLE can occur at any age, although it becomes more frequent after five years of age and is increasingly prevalent after the first decade of life.

Method

The authors present a case report of a 14-teen year old girl, first examined in 2016 for primary hypothyroidism and subsequently diagnosed for SLE with mucocutaneous and hematologic involvement.

Results

Besides thyroid failure symptoms (fatigue, cold intolerance, weight loss, 4 kgs in the last 3 months and constipation), she complained for alopecia, oral ulcers and joint pain. General laboratory assessment reveled normocytic anemia (9,6 g/dl) with thrombocytopenia (129 000 /mm3), high sedimentation rate (54mm), immunofluorescence antinuclear antibody (ANA) screening with a high titer (>640) homogeneous pattern with dsDna, nucleosomes and histones positive antibodies.

Conclusion

Disease course in childhood SLE may be more severe, and certain cutaneous manifestations may have a stronger link with systemic disease. Photosensitivity, arthritis/polyarthritis, arthralgia, and fever may be the presenting symptoms. Childhood onset patients are more likely to have severe organ involvement, especially nephropathy. Other major manifestations, such as neurologic involvement, thrombocytopenia and hemolytic anemia, are also common initial features in the childhood onset group.

AUTO1-0561
SLE, SJÖGREN'S DISEASE

ANTI-DSDNA TESTING: ENZYME IMMUNOASSAY VS INDIRECT IMMUNOFLUORESCENCE?

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Background

Systemic lupus erythematosus (SLE) is an autoimmune multisystemic chronic inflammatory disease. All the classification and diagnosis criteria issued so far have been including anti-dsDNA testing as an important serologic criteria for diagnosis, accounting for its 100% clinical sensitivity, without any mandatory reference regarding a defined method.

Method

The authors present revised data, since 2014, concerning positive results on anti-dsDNA testing, in a reference autoimmune laboratory, using an algorithm that includes fluoroenzymoimunoassay (FEIA) as screening technology followed by CLIFT assay technology for confirmation of positive previous results on CLIFT.

Results

The 2013 published paper “International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies” recommends that a ANA positive result, in the context of SLE, should be followed by anti-dsDNA testing;

Conclusion

The reference testing for anti-dsDNA antibody determination are the Farr assay and the CLIFT because of their high clinical specificity. It is also referred that in case of using any other alternative methods it is recommended that positive results should be confirmed by CLIFT or Farr assay and these should be reported separately.

AUTO1-0957
SLE, SJÖGREN'S DISEASE

ISOLATION AND CHARACTERIZATION OF AUTO-REACTIVE B-CELLS IN SLE PATIENTS BY USING EXTRACTABLE NUCLEAR ANTIGENS (ENA)-BOUND IMMUNOBEADS

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Background

B cell hyperactivation and auto-antibody (Ab) production are hallmarks of SLE. However, the contribution of autoreactive mature B-cells (BC) to autoAb production is not completely known.
Our objective is to detect circulating ENA-specific-BC (ENA-BC) and to explore their capability to differentiate into ENA-specific-Ab-secreting cells (ENA-ASC).

Method

Blood ENA-BC from 26 SLE patients with serum anti-ENA autoAb were sorted by using magnetic immunobeads bearing ENA (QUANTA-Flash®-ENA7, Werfen). As a control, anti-citrullinated peptides (ACPA)-specific BC were purified from 5 patients with Rheumatoid arthritis (RA) and serum ACPA.
Anti-CD40 mAb and a mix of BC-inducing cytokines were used to stimulate isolated ENA-BC. In cultures, anti-ENA Ab and IgG production were determined by chemiluminescence and ELISA, respectively. ASC were identified as cells with a plasmablast morphology and intracytoplasmic IgG by immunofluorescence. Phenotype of ENA-BC was performed by flow cytometry.

Results

In 14/26 patients, ENA-specific BC circulated and differentiated into ENA-ASC in stimulated cultures. Control ENA-BC cultures did not show anti-ENA Ab secretion. Also, ENA-BC, but not ACPA-BC, were induced to produce anti-ENA Ab, and vice versa. More than 70% of ENA-BC were CD20+CD27- and more than 10% of them expressed CD69.

Conclusion

Immunoselection by using magnetic immunobeads coupled to ENA and ACPA is a reliable method for purifying ENA and APCA-specific BC from SLE and RA patients, respectively.
ENA-BC circulated in 53% of the SLE patients and they were induced to secrete anti-ENA Ab under stimulation.

AUTO1-0671
SLE, SJÖGREN'S DISEASE

BONE METABOLISM MARKERS, BONE MINERAL DENSITY AND CARDIOVASCULAR CALCIFICATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Cardiovascular disease due to accelerated atherosclerosis represents a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Osteoporosis is also frequently associated with SLE. The aim of our study was to evaluate the association between bone metabolism markers, vascular calcifications and bone mineral density in SLE patients.

Method

Female patients with SLE were enrolled after inform consent and underwent multislice computed tomography, carotid ultrasound imaging, abdominal aorta ultrasound, leg arteries ultrasound and echocardiography to assess the presence of vascular calcifications. Dual-energy X-ray absorptiometry was performed to measure bone mineral density (BMD) in lumbar spine and hip. Receptor activator of nuclear factor kB ligand (RANKL), osteoprotegerin (OPG), osteocalcin, fetuin-A and C telopeptide of collagen were quantified in serum of SLE patients.

Results

We included 70 SLE patients. The mean age at inclusion was 45.7 (± 13.7) years, and the median disease duration was 7.2 [2.1-13] years. Vascular calcifications in at least one arterial territory were detected in 45.7% of the SLE patients: 22.8% with coronary artery calcifications, 28.5% with thoracic aorta calcifications, 24.2% with abdominal aorta calcifications, 5.7% with leg arteries calcifications and 8.5% with carotid artery calcifications. There was a mild correlation between OPG and the extent of arterial calcifications (rho = 0.3, p = 0.011, Spearman correlation test). We didn’t find any correlation between decreased BMD and arterial calcification.

Conclusion

We found a correlation between OPG and the extent of the arterial calcifications in SLE patients. In our population, there was no association between osteoporosis and arterial calcifications.

AUTO1-0513
SLE, SJÖGREN'S DISEASE

INTERFERON-BETA DOWN-MODULATES NITRIC OXIDE PRODUCTION AND INDUCIBLE NITRIC OXIDE SYNTHASE EXPRESSION DURING PRIMARY SJOGREN'S SYNDROME

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Background

Sjögren's syndrome (SS) is a type of autoimmune epithelitis characterized by mononuclear cell infiltration of the exocrine tissues. It may occur alone as primary (pSS) or develop out of a connective tissue disease, known as secondary. This syndrome is associated with an autoimmune disorder which appears with secretion of inflammatory mediators such as nitric oxide (NO). The overproduction of NO could contribute to the pathology seen in pSS. Herein, we studied the effect of interferon-beta (IFN-β) on NO production and iNOS expression in peripheral blood mononuclear cells (PBMC) from pSS patients and healthy controls.

Method

PBMCs isolated from Algerian pSS patients (n=46) and healthy controls (n=19) were treated (or not) with IFN-β. NO production was estimated with the Griess method. Expression of iNOS in PBMCs was examined by fluorescence immunostaining.

Results

Higher levels of NO were detected in plasma of pSS patients compared with healthy controls. Interestingly, our findings also revealed that IFN-β decreases both NO production and NOS2 expression. The immunosuppressive effect of IFN-β in pSS may be partly due to suppression of iNOS expression.

Conclusion

Collectively, our results highlight the immunomodulatory effect of IFN-β which can be considered as a valuable candidate in the intervention of pathological inflammation seen in primary Sjögren's syndrome.

AUTO1-0767
SLE, SJÖGREN'S DISEASE

IDIOPATHIC THROMBOCYTOPENIC PURPURA HIDING SYSTEMIC LUPUS ERYTHEMATOSUS - CASE REPORT

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Background

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystem involvement. Although the blood abnormalities are common, the are only few cases described in literature of association between SLE and thrombocytopenic purpura.

Method

36 years old female with a recent medical history of high intestinal obstruction check in with malaise, malnutrition, nausea and vomiting. She was previously diagnosed in with hemolytic anemia and idiopathic thrombocytopenic purpura (TIP). At that moment she was not responding to Rituximab (anti CD20 Ab) but was a responder to Eltrombopag.

Results

Clinical examination at admission revealed cachexia, pale skin, lower limb ecchymosis, bilateral calves' edemas, dullness in the inferior 2/3 of the right hemi thorax, tachycardia, increased abdominal volume due to ascites.

The laboratory results showed anemia, low white blood cell counts, low complement levels, extreme low platelet counts (9000/mm3), low protein levels, positive anti DNA Antibodies). Due to the association of hematological abnormalities with serositis, low complement and positive anti dsDNA the patient met SLICC Criteria for lupus. Thrombocyte mass transfusions were administered in combination with cortisone for a short period, with no result She was then successfully treated with high doses of cortisone, Danazol, an androgenic hormone, Eltrombopag and Hidroxicloroquine.The mixed mechanism of the malnutrition (lupus enteropathy and the post surgically lack of digestive mucosa stimulation) was treated with i.v. nutrition and albumin transfusion.

Conclusion

The TIP as a debut of SLE is extremely rare and the efficient treatment could be a real challenge.

AUTO1-0414
SLE, SJÖGREN'S DISEASE

HEMATOLOGICAL MANIFESTATIONS IN A SINGLE CENTER COHORT OF SLE PATIENTS

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by overproduction of autoantibodies associated with a hyperactivity of B cells. The tissue involvements associated with SLE include also numerous hematological manifestations, which are often overshadow by major organ involvement. The aim of the study was to assess the incidence of hematological symptoms and their frequency in patients with SLE.

Method

Single-center, retrospective study analyzed the incidence of hematological manifestations in 160 lupus patients meeting SLICC classification criteria for SLE. The presence and pattern of hematological manifestations was compared at the onset of the disease, during its course and at the remission. The data were statistically analyzed.

Results

Hematological manifestations were present in 67% of patients with SLE. The most common one, anemia, occurred early in the disease in 45% of patients with hemoglobin (Hb) level of 101±13 g/l and average erythrocytes numbers $3.5x10^{12}$/l. After the stabilization of the disease the incidence of anemia decreased to 20% with a mean Hb value of 123 g/l. Hemolysis was found in 21% of patients with anemia. Leucopenia was present in 24% of patients, the mean number of leucocytes in those patients was 2.71x 10^9/l. Twenty four % of patients had thrombocytopenia and antiphospholipid syndrome was present on 16% of lupus patients.

Conclusion

The hematological manifestation are very common among lupus patients. Anemia, which affects almost half of the patients, was the most frequent abnormality found in our cohort.

AUTO1-0541
SLE, SJÖGREN'S DISEASE

DIFFERENT EXPRESSION OF ANTI-RO52/TRIM21 AND ANTI-RO60/SS-A ANTIBODIES IN VARIOUS DISEASE COHORTS AND IMPLICATION FOR TESTING

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Background

Historically anti-Ro52/TRIM21 and anti-Ro60/SS-A antibodies were described as a unique autoantibody system and collectively referred to as anti-SS-A. However, subsequent studies indicated that anti-Ro52 and Ro60 antibodies exhibit different expression in various disease conditions. Anti-Ro60/SS-A antibodies are reported to have a strong clinical association with Sjögren's Syndrome (SjS) and systemic lupus erythematosus (SLE) while anti-Ro52/TRIM21 antibodies have limited diseases specificity (Schulte-Pelkum et al.). However, anti-Ro52/TRIM21 antibodies are important biomarkers in a spectrum of autoimmune processes, including idiopathic inflammatory myositis (IIM), systemic sclerosis (SSc) and interstitial lung disease (ILD).

Method

A total of 1693 samples were collected from various diseases. Antigens were coupled to paramagnetic particles and tested using a novel bead based immunoassay (Inova Diagnostics, USA, research use only). Statistical analysis (Fisher exact test, receiver operating characteristics (ROC) analysis) was done with ANALYSE-IT Version 4.90.

Results

Higher prevalence of anti-Ro52/TRIM21 and anti-Ro60/SS-A antibodies were found in SjS and SLE, respectively. The prevalence of anti-Ro52/TRIM21 and anti-Ro60/SS-A antibodies was similar in SjS and SLE, but significantly different in IIM, SSc and PBC (see table below). On the specificity side, values of 96.9% (94.7-98.2%) and 96.6% (94.4-98.0%) were found for the anti-Ro52/TRIM21 and anti-Ro60/SS-A, respectively.

Antibody	SLE (95% CI)	SjS (95% CI)	SSc (95% CI)	IIM (95% CI)	PBC (95% CI)
Ro60/SS-A	37.5% (32.8-42.3%)	62.8 % (53.9-70.9%)	0.0 % (0.0-0.2%)	9.9% (6.6-14.7%)	14.2 % (9.8-20.1%)
Ro52/TRIM21	32.2 % (27.7-36.9%)	63.9 % (54.8-71.7%)	14.7 % (10.7-19.9%)	18.4 % (13.8-24.2%)	33.0 % (26.4-40.2%)

Conclusion

Our study confirms the notion that anti-Ro52/TRIM21 and Ro60/SS-A antibodies are differently expressed in various disease cohorts, a finding that underscores their independent clinical associations and also the importance to test these biomarkers separately.

AUTO1-0491
SLE, SJÖGREN'S DISEASE

UNEXPECTED CAVITARY LESIONS IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown origin which may affect many different organs and lead to diverse outcomes. Pulmonary involvement though infrequent in pediatric SLE may sometimes be life-threatening, thus prompt and aggressive treatment is mandatory. Cavitary lung lesions are rarely reported in SLE and even less frequently attributed to primary manifestations of the disease itself but rather to other causes

Method

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Results

We report a case of 17-year-old female who recently presented with chronic fatigue, autoimmune hemolytic anemia and pulmonary alveolar hemorrhage. According to ACR/SLICC criteria diagnosis of SLE was established and after intensive treatment with pulse methylprednisolone and plasma exchanges her condition was stabilized. On the 17th day, fine crackles in both lungs were observed following an increase in acute phase reactants. The chest revealed four bilaterally located cavitary nodules, one had a necrotic central with a 3-cm diameter in CT. Immunesuppressive treatment was discontinued and she was started on vancomycine, meropenem, trimethoprime-sulfometaxazole and oseltamivir but with no clinical improvement. Extensive infectious workup was negative including blood, pleural and bronchoalveolar fluid cultures and PCR assessment for bacteria, fungi, mycobacteria and viral pathogens. A tuberculin test and Quantiferon-TB-Gold were both negative. Bronchoalveolar lavage cytology showed no malignant cells but hemosiderin laden macrophages were detected. SLE activation was considered. Immunesuppressive treatment with mycophenolate mofetil and pulsemethylprednisolone was initiated which induced clinical and radiological improvement.

Conclusion

A cavitary lung lesion associated with SLE activation is extremely rare but should always be kept in mind to avoid life-threatening complications.

AUTO1-0383
SLE, SJÖGREN'S DISEASE

INVESTIGATING THE SUBSETS OF CIRCULATING FOLLICULAR T HELPER CELLS IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

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Background

Despite ongoing studies, the pathogenesis of primary Sjögren's syndrome (pSS) remains unclear. We have already known that pronounced B-cell hyperactivity with increased levels of high-affinity autoantibodies are the hallmark of the disease, but careful attention is currently being paid on the role of follicular T helper (T_{FH}) cell subsets in pSS.

Method

Up to the present, 32 patients with pSS and 21 controls were enrolled in the study. Immunophenotyping of T_{FH}-cells, T_{FH} subsets, T_{FR}-cells, and B-cell subsets were performed by flow cytometer.

Results

We observed higher percentages and numbers of naive B-cells and transitional B-cells in pSS, while memory B-cells showed decreased frequencies and numbers in pSS compared to controls. These results were more conspicuous in patients with EGMs or SSA positivity. Patients with more severe disease course had elevated ratio of activated T_{FH}-like cells compared to controls. Among the $CD4^+CXCR5^+$ T_{FH}-cells, $T_{FH}2$-cells were the main subset which significantly decreased in pSS patients with EGMs compared to controls as well as patients without EGMs in percentages and numbers. The percentages and numbers of T_{FR}-cells were lower in pSS compared to controls. We revealed a significant positive correlation between $T_{FH}1$-cells and non-switched memory B-cells and primarily memory B-cells, moreover this subset also showed a significant positive correlation with serum levels of IgG and immune-complexes.

Conclusion

In conclusion, these results reinforce previous observations with B-cells and extend our knowledge regarding T_{FH}-like cells. Various results have been published with the distribution of T_{FH}-cell subsets in autoimmune diseases and we intended to elucidate the controversy in pSS.

AUTO1-0833
SLE, SJÖGREN'S DISEASE

CAROTID AND FEMORAL ATHEROSCLEROSIS IN ANTIPHOSPHOLIPID SYNDROME: EQUIVALENT RISK WITH DIABETES MELLITUS IN A CASE-CONTROL STUDY

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Background: Antiphospholipid syndrome (APS) may carry a worse prognosis for vascular complications when co-existing with subclinical atherosclerosis, however, the association between the two conditions remains ambiguous.

Methods: We evaluated ultrasonographic markers of subclinical atherosclerosis in carotid and femoral arteries of 86 patients with thrombotic APS (43 primary APS (PAPS), 43 systemic lupus erythematosus-associated APS [SLE/APS]), 86 patients with diabetes mellitus (DM) and 86 healthy controls, individually matched for age and gender, and investigated their associations with traditional and disease-related factors in APS.

Results: Carotid plaques were found in 28% of PAPS, 23% of SLE/APS, and 30% of DM patients versus 9% of controls (p=0.006). Femoral plaques were found in 33% of PAPS, 19% of SLE/APS, 20% of DM, and 9% of controls (p=0.032). Multivariate regression-derived relative risk estimates for atherosclerotic plaques in any location were 2.72 for PAPS, 2.63 for SLE/APS, and 1.98 for DM (p=0.004, 0.009, 0.032 respectively), after adjusting for age, gender, hypertension, dyslipidemia, smoking, BMI, and family history of coronary disease. Among patients with APS, atherosclerotic plaques were associated with the number of traditional CVD risk factors in both PAPS (RR=2.75, p<0.001) and SLE/APS (RR=1.84, p<0.001), and with IgG anti-beta2-glycoprotein I antibodies in SLE/APS.

Conclusions: Patients with PAPS and SLE/APS have a nearly 2.5-fold risk of atherosclerotic plaques in carotid and femoral arteries compared to healthy controls, similar to DM patients. Atherosclerotic plaques are associated with the number of traditional risk factors in both APS and SLE/APS, and with IgG anti-beta2-glycoprotein I antibodies in SLE/APS.

AUTO1-0140
SLE, SJÖGREN'S DISEASE

PLASMAPHERESIS IN SYSTEMIC AUTOIMMUNE DISEASES

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Background

Autoimmune diseases correspond to a diverse and complex group of pathologies with a broad clinical spectrum including autoantibodies production. Plasmapheresis is a valid option for the management of critical patients in addition to immunosuppressive treatment. The aim of this study is to describe the main clinical characteristics and outcomes of patients with systemic autoimmune diseases who received management with plasmapheresis.

Method

A descriptive study was carried out, including patients with systemic autoimmune diseases who received plasmapheresis.

Results

A total of 66 patients were included. The average age was 33.5 years, the majority of patients were female n=51 (77.27%). Forty (60.61%) patients had Systemic Lupus Erythematosus (SLE) followed by ANCA-associated vasculitis in 12 cases (18%). The main indication for plasmapheresis in SLE was diffuse alveolar hemorrhage (DAH) in 20 (30.3%) cases, followed by neurolupus in 9 (13.6%) (**Table 1**). Any patient died from plasmapheresis complications. The main adverse event was bleeding, without differences according to the type of plasmapheresis solution. The overall outcomes were improvement in 41 patients (62.12%) **(Table 2)**.

Table 1. Most frequent pathologies and indications of plasmapheresis

SLE	**40 (60.61)**
DAH	11 (27.5)
Neurolupus	9 (22.5)
Thrombotic microangiopathy without APS	5 (12.5)
CAPS	4 (10)
Lupus Nephritis (Type IV)	4 (10)
Other indications	7 (17.5)
ANCA-associated vasculitis	**12 (18.18)**
DAH	6 (50)
Rapidly progressive glomerulonephritis	6 (50)
Inflammatory myopathies	**3 (4.54)**
Systemic sclerosis	**2 (3.04)**
Others	**9 (13.6)**
Total	**66**
Average of TPE sessions **	5.39 (3-14)

TPE: Therapeutic plasma Exchange; SLE: Systemic Lupus Erythematosus; APS: Antiphospholipid syndrome; DAH: Diffuse alveolar hemorrhage; CAPS: Catastrophic Antiphospholipid syndrome
** Median(RIC)

Table 2. Main indications and outcomes of plasmapheresis

TPE indication/Outcome	Improvement - N. patients (%)	Unchanged - N. patients (%)	Worsening - N. patients (%)	Total	Death - N. patients (%)	Dialysis
DAH	11 (55)	2 (10)	7 (35)	20	7 (35)	3 (15)
Neurolupus	7 (78)	1 (11)	1 (11)	9	1 (11)	1 (11)
Rapidly progressive glomerulonephritis	5 (71)	2 (29)	0	7	0	3 (60)
CAPS	4 (80)	0	1 (20)	5	1 (20)	0
Others	14 (56)	8 (32)	3 (12)	25	3 (12)	4 (16)

DAH: Diffuse Alveolar Hemorrhage; CAPS: Catastrophic Antiphospholipid syndrome

Conclusion

Plasmapheresis is a safe and effective procedure in patients with severe autoimmune diseases, despite this there is a lack of studies that provide more information about the number of sessions and type of plasma exchange that should be used.

AUTO1-0238
SLE, SJÖGREN'S DISEASE

CCL22-PRODUCING RESIDENT MACROPHAGES ENHANCES INFLAMMATION IN SALIVARY GLANDS OF SJOGREN'S SYNDROME

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Background

Sjögren's syndrome (SS) is an autoimmune disease that affects lacrimal and salivary glands characterized by diffuse lymphocyte infiltration. Although the contribution of T or B lymphocytes to the pathogenesis of SS has been described, the role of the other immune cells remains unclear.In this study, to clarify the role of macrophage in the onset or development of SS, we analyzed the distribution and function of macrophages in salivary glands of a murine model.

Method

We used NFS/*sld* mice tymectomized on day 3 after birth as SS model.

Results

Macrophages in the salivary glands of SS model mice were classified into two phenotypes, $F4/80^{+}CD11b^{high}$ and $F4/80^{+}CD11b^{low}$. $CD206^{+}$ resident macrophages were included in the $F4/80^{+}$ $CD11b^{high}$ population and phagocytic activity was significantly enhanced in this population. In comprehensive gene analysis by PCR-array, chemokine gene expression was different between the two subsets of macrophage in salivary glands. Up-regulation of several macrophage-related genes was found in the $F4/80^{+}CD11b^{high}$ macrophages. Among them, CCL22 produced by the resident macrophages played important roles in the migration, activation, or differentiation of T cells in the target organ to accelerate autoimmunity. In addition, CCR4 expression, the receptor for CCL22, on effector T cells was enhanced in salivary glands of SS model mice. Furthermore, autoimmune lesions in the target organs of SS model mice were prevented by administration of anti-CCL22 antibody.

Conclusion

These findings suggest that the unique subsets of macrophage in the salivary glands may contribute to onset or development of SS.

AUTO1-0525
SLE, SJÖGREN'S DISEASE

C-REACTIVE PROTEIN +1444CT (RS1130864) GENETIC POLYMORPHISM IS ASSOCIATED WITH THE SUSCEPTIBILITY TO SYSTEMIC LUPUS ERYTHEMATOSUS AND C-REACTIVE PROTEIN LEVELS

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Background

The role of the T allele of +1444CT (rs1130864) polymorphism of C-reactive protein (CRP) on systemic lupus erythematosus (SLE) susceptibility and on CRP levels in SLE patients remains uncertain. The aim of this study was to evaluate the association between the rs1130864 CRP polymorphism with SLE susceptibility, disease activity, and CRP levels.

Method

The study enrolled 176 Brazilian patients and 137 controls. SLE disease activity was assessed using the SLE Disease Activity Index (SLEDAI). The rs1130864 CRP polymorphism was determined using PCR-RFLP.

Results

SLE patients presented higher body mass index (p = 0.046) and CRP levels (p = 0.017) than controls. The genotype and allele frequencies of patients differed from controls [CC vs. CT = odds ratio (OR) 1.730, 95% confidence interval (CI) 1.068-2.803, p = 0.035; CC vs. TT = OR 3.667, 95% CI 1.410-9.533, p = 0.009; C vs. T = OR 1.883, 95% CI 1.299-2.728, p = 0.001)]. Patients carrying the T allele presented higher CRP levels (p = 0.009), were more frequent Caucasians (p = 0.018), and with no use of immunosuppressive treatment (p = 0.004) than those carrying the C allele. The SLEDAI and anti-double-stranded DNA positivity did not differ from those carrying T vs. C allele (p = 0.595 and p = 0.243, respectively).

Conclusion

The rs1130864 CRP polymorphism was associated with SLE susceptibility and CRP levels, but not with disease activity, suggesting that this polymorphism may participate in the pathophysiology of SLE through increasing the CRP that, probably, plays an inflammatory role in SLE pathophysiology.

AUTO1-0818
STANDARDIZATION OF DIAGNOSTICS

DISCORDANCE BETWEEN THREE AUTOANTIBODIES DETECTION METHODS

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Systemic autoimmune diseases are characterized by development of different autoantibodies against intracellular antigens. In systemic lupus erythematosus (SLE), autoantibodies found in patients's serum are mainly against nuclear antigens. The most frequent autoantibody observed on SLE patients are the anti-double strand DNA antibodies (anti-dsDNA) followed by autoantibodies against extractable nuclear antigens (ENAs) which are soluble cytoplasmic and nuclear components with over 100 different antigens described. ENAs are also present in patients with Sjogren´s Syndrome (SS) in which anti-Ro and Anti-La are the more frequent. Thus, cost-effective methods for screening large amount of autoantibodies are of key interest.
The aim of our study was to compare three methods for detecting nuclear autoantibodies in 87 patients (56 with established SLE and 31 with established SS). We performed conventional ELISAs (Inova) for measurement of anti-dsDNA, anti-Ro, anti-La, anti-RNP and anti-Sm antibodies. Simultaneously, autoantibodies were assessed either by IMTEC-ANA-LIA Maxx (Human diagnostics) or by ANA-Profile 23 (Euroimmune), an easy- to-use screening assay, consisting of a nitrocellulose membrane containing up to 23 antigens on line, an attractive method in term of cost-effectiveness.
Although in three cases level of agreement was "Good/ Very good", the discordance between methods was striking, with levels of agreement moderate, fair or even poor. Overall, the best agreement was found between ELISA and ANA-LIA maxx (Table 1). Our data reveal an enormous discordance in the results among these autoantibodies-detection methods, and highlight the necessity to standardize novel methods to yield reliable results independently of the method.

CI: confidence interval.

AUTO1-0314
STANDARDIZATION OF DIAGNOSTICS

PERFORMANCE OF AUTOMATED INDIRECT IMMUNOFLUORESCENCE EVALUATION OF ANTINUCLEAR AUTOANTIBODIES

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Background

Indirect immunofluorescence is still the gold standard for the detection of antinuclear antibody (ANA) . However conventional technique is subjective, requiring skilled experts. Growing demand for ANA testing, there is a need for advanced automated systems. EUROPattern Suite (Euroimmun AG, Lubeck, Germany) system seems to be a solution by reducing labarotory workload, also preventing interpretation bias. This study was conducted to analyze the performance of EUROPattern Suite (EPa) for ANA testing.

Method

Sera were prepared on slides covered with Hep-20-10 and primate liver cells by the IF-Sprinter device with a starting diluton of 1:100. Results obtained by the EPa system which was initially optimized for the reader were compared with the evaluation of the expert according to digital images.

Results

Among 575 samples, 529 (92% agreement) were classified as ANA positive/ negative both by EPa and expert (Table 1). In regard to pattern reading overall sensitivity and specificity of the EPa were 95% and 96%, respectively (Table 2). Table 3 clearly shows that false positive results detected by the Epa were mostly in 1/100 titer.

Conclusion

- There was an agreement of 92% between the EPa and expert for ANA reading.
- With a high concordant results for patterns and titers, sensitivity and specificity of EPa were 95% and 96%, the highest agreement was observed for nuclear dots and centromere patterns.
- Incoherent EPa results with the expert in regard to pattern reading may be prevented by software optimization.
- Automated reading results seems not to be satisfactory for clinical reporting and needs final evaluation of the expert.

Table 1: Comparison of EPa and expert reading for ANA testing

EPa	Expert		Total
	Negative	Pozitive	
Negative	113	0	113
Positive	46	416	462
Total	159	416	575

Concordance: 92%

Table 2 : Simple pattern coherence in EUROPattern Suite

	ANA Patterns	Homogenous	Granular	Nucleolar	Centromeres	Nuclear dots	N.Membrane	Cytoplasmic	Total
		179*	338*	33*	24*	32*	24*	56*	
EPa	True positive	171	327	29	23	32	18	51	651
	False negative	8	11	4	1	0	6	5	35
	True negative	332	192	537	550	542	550	511	3214
	False positive	64	45	5	1	1	1	8	125
	Sensitivity	95,5%	96,7%	87,9%	95,8%	100,0%	75,0%	91,1%	95%
	Specificity	83,8%	81,0%	99,1%	99,8%	99,8%	99,8%	98,5%	96%

*Reading results of the expert

Table 3: False positive results in titers based on patterns in EUROPattern Suite

			threshold value 1/100	>1/100 - <1/320	≥1/320 - <1/1.000	≥ 1/1.1000
		n	(+)	+	++	≥ +++
EPa	Homogenous	64	58	2	2	2
	Granular	45	44	1	0	0
	Nucleolar	5	3	2	0	0
	Centromeres	1	1	0	0	0
	Nuclear dots	1	0	0	0	1
	N.Membrane	1	0	1	0	0
	Cytoplasmic	8	7	1	0	0
	Total (%)	125 (100)	113 (90)	7 (6)	2 (2)	3 (2)

AUTO1-0509
STANDARDIZATION OF DIAGNOSTICS

ANTIBODY TITRATION WITH A COMPLETE AUTOMATED PLATFORM

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Background

The IIF using the HEp-2 cell substrate should be still considered the “gold standard” techniques for determination of antinuclear antibodies. Standardization and automation can be considered to be still in progress.
AIM: To evaluate the performance of Helios platform (Aesku, Germany) for the discrimination of ANA positive from ANA negative samples and the capability to estimate the endpoint titer prediction (EPT). The EPT is defined as the highest dilution in which staining intensity is still detectable.

Method

We examined 167 unselected sera from our routine on Helios platform (Aesku Diagnostics). Helios analyzed four images per well and assigned the positivity when at least three images were positive. We performed all the positive samples up to a dilution above the estimated titration.

Results

97/164 (59.1%) samples were classified by the system as negative, 67/164 (40.9%) were positive from 1:80 to 1:5120. 5/67 (7.5%) diluted samples disagree with the end point titer (EPT) proposed by Helios. Discrepant results were: 2 centromeric, 1 nucleolar, 1 nuclear membrane, 1 cytoplasmic mithocondrial pattern.

Conclusion

After the first screening run, a titration of positive samples is strongly recommended. The Helios EPT estimate an endpoint titer for wells that were pre-classified as positive in a previous screening.

The discordance observed between the EPT proposed and the real final dilution is, maybe, due to the particular pattern of these samples (Centromere, Nucleolar, Cytoplasmatic).

The EPT of Helios platform could improve laboratory efficiency, reduce laboratory variability and support standardization of IIF especially in high throughput laboratories.

AUTO1-0417
STANDARDIZATION OF DIAGNOSTICS

SYSTEMATIC COMPARISON OF THREE DIFFERENT HEP-2 CELL SYSTEMS FOR DETECTION OF ANTI-NUCLEAR ANTIBODIES

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Background

The gold standard for detection of anti-nuclear antibodies (ANA) represents indirect immunofluorescence (IIF) using HEp-2 cells as a substrate. Different HEp-2 cell systems are commercially available requiring verification before introduction into routine diagnostics.

Method

We compared HEp-2 cells purchased from 3 manufacturers (Theradiag; A. Menarini Diagnostics; Aesku Diagnostics) among serially diluted serum samples (1:80, 1:160, 1:320, 1:640, 1:1280) of 37 patients suffering from systemic autoimmune diseases by manual IIF. Each slide was subjected to fluorescence pattern and titer recognition using two independent observers.

Results

Pattern recognition and end point titer did no significantly differ between observers. Twenty-three of 37 patient samples (62.2 %) showed qualitative and quantitative agreement of HEp-2 results whereas in 14 of 37 samples (37.8%) discrepancies were identified. Disagreement included the mitotic fluorescence pattern in 6 patients (16.2%), the cytoplasmic pattern in 4 patients (10.8%) and the nuclear pattern in 5 patients (13.5%). Moreover, in one patient discrepancies both of the nuclear and the cytoplasmic pattern were observed. As compared to concordant results among two manufacturers A. Menarini cells disagreed in 7 cases, Theradiag cells in 5 and Aesku cells in 3 cases, respectively.

Conclusion

The present study demonstrates high concordance of results obtained by manual IIF between observers. However, the HEp-2 cell systems under investigations frequently revealed clinically relevant diverging fluorescence patterns. Therefore, standardization of ANA-cell systems is urgently required.

AUTO1-0325
STEM CELL THERAPY IN AUTOIMMUNE DISEASES

IMMUNOLOGICAL PARAMETERS DYNAMICS IN PATIENTS WITH MULTIPLE SCLEROSIS AFTER SINGLE AND REPEATED INTRAVENOUS INFUSION OF AUTOLOGOUS MESENCHYMAL STEM CELLS

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Background

Preliminary results of mesenchymal stem cells (MSCs) application in multiple sclerosis (MS) show the efficacy and safety, but the characteristics of MSCs immunomodulatory effect still remains an issue. The aim was to estimate the lymphocytes subsets number dynamics and proliferation rate in MS patients after single and repeated intravenous autologous MSCs infusion.

Method

Peripheral blood was obtained from relapse-remitting MS patients (n=14) with expanded disability status scale (EDSS) score of 2.5 (2.0÷3.5) at baseline and 10 days, 1, 3, 6, 9, 12 months after single (n=7) and repeated (n=7) therapy. Autologous bone marrow-derived MSCs were infused intravenously (1.55 (0.92÷2.35) × 10^6 cells/kg). Phenotype and proliferation were monitored using flow cytometry.

Results

After single MSCs infusion, the decrease of $CD4^+CD45RO^+$T-cells and γδT-cells upregulation was established on day 10 ($p<0.01$) and persisted during the monitoring, while the reduction of $CD8^+CD45RO^+$T-cells and $CD56^+$NK-cells ($p<0.05$) was observed 3 months after repeated administration. MSC-mediated selective immunosuppression of myelin-specific T-cell proliferation was demonstrated 9 months after single infusion (39,1% (11,8%÷45,0%)). Repeated MSCs-based cell therapy supported the immunosuppressive effect that correlated with decreased EDSS and demyelination foci as well as increased retinal nerve fiber layer thickness ($p<0.05$).

Conclusion

The clinical efficacy of MSCs therapy was demonstrated in MS patients in the both early and late post-transplanted periods. Repeated MSCs administration is reasonable within 9-12 months after the first infusion for supporting the pathogenic cell therapy effect in MS patients.

AUTO1-1056
STEM CELL THERAPY IN AUTOIMMUNE DISEASES

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR SYSTEMIC SCLEROSIS – A TREATMENT TO BE CONSIDERED

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Background

Systemic sclerosis (SSc) is a multisystem disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs. The etiology and pathogenesis of the scleroderma disorders are poorly understood. As a result, treatment of these condition is difficult.
Studies of Immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation (AHSCT) have demonstrated efficacy in preventing disease progression in SSc patients. However, the high incidence of treatment-related mortality has limited its use in management of SSc. Careful selection of patients with SSc for this kind of treatment is of key importance.

Method

The authors describe 3 cases of difuse SSc, 1 with severe esophagogastric dysmotility and 2 with pulmonary interstitial disease, in patients aged 20, 42 and 46 respectively, refractory to immunosuppressive therapy who underwent AHSCT with improved skin thickness, pulmonary function, gastro-intestinal mobility and quality of life.

Results

Randomized trials have showed statistically significant clinical benefits and long-term benefits after AHSCT in patients with scleroderma, including improved event-free and overall survival at a cost of increased expected toxicity and treatment-related mortality in the first year.

Conclusion

With this cases the authors would like to emphasize the use of AHSCT as a valid and successful treatment for SSc, and the importance of a timely referral and careful selection of patients.They also consider relevant their use not only in cases of pulmonary involvement, but also other progressive forms of the disease with severe diffuse cutaneous and visceral involvement in which there is no previous response to conventional pharmacological therapy.

AUTO1-0941
STEM CELL THERAPY IN AUTOIMMUNE DISEASES

MESENCHYMAL STEM CELLS MITIGATE INFLAMMATORY BOWEL DISEASE BY SUPPRESSION OF INFLAMMATION AND OXIDATIVE STRESS

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Background

Inflammatory bowel disease (IBD) is a complex immunological disorder characterized chronic inflammation caused by mainly unknown factors. The interleukin-10 knockout (IL-10 KO) mouse is a well-established murine model of IBD which develops spontaneous intestinal inflammation that resembles Crohn's disease. Oxidative stress is considered a leading cause of cell and tissue damage.Reactive oxygen species (ROS) itself can cause direct cell injury and/or cause indirect cell injury by secretion of cytokines from damaged cell.

Method

In this study, human bone marrow-derived mesenchymal stem cells (MSCs) was injected to IL-10 KO mice (MSC) and oxidative stress and inflammation levels as well as histological changes were evaluated in the large intestine and compared with those of control IL-10 KO mice (CON).

Results

The levels of ROS (superoxide and hydrogen peroxidase) and secondary end product of lipid peroxidation (malondialdehyde) were significantly higher in CON but superoxide dismutase (SOD) and catalase levels were higher in MSC. Inflammation related markers (INF-γ, TNF-α, IL-4, and CD8) expression and inflammatory changes in histological analysis were much milder in MSC.

Conclusion

We conclude MSCs decrease oxidative stress in IL-10 KO mice and this lead to suppression of IBD. This study supported by National Research Foundation of Korea (2017R1A3B03032090).

AUTO1-0263
STEM CELL THERAPY IN AUTOIMMUNE DISEASES

MESENCHYMAL STEM CELLS IMMUNOSUPPRESSIVE PROPERTIES AND CHARACTERISTICS OF CELL THERAPY IMMMUNOMODULATORY EFFECT IN MULTIPLE SCLEROSIS

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Background

Mesenchymal stem cells (MSC)-based therapy becomes a promising approach in multiple sclerosis (MS) when a key role is played by myelin-specific T-lymphocytes. Proper characteristics of MSC immunomodulatory mechanisms is crucial to anticipate a possible effect of MSC therapy.

Objective. To develop the criteria for evaluating *in vitro* MSC immunosuppressive properties and to assess cell therapy effect after autologous MSC transplantation in MS patients.

Method

25 MS patients with *EDSS* of 3,76(1,5÷7,5) were enrolled. Patients with relapse-remitting MS (n=12, f:m–6:6), age–33,0(25,5÷35,5) years, with *EDSS* of 2,75(2,00÷3,25) received intravenous autologous bmMSC (1,55(0,92÷2,35) cells/kg).

Immunological parameters were estimated by flow cytometry using a model of *in vitro* cocultivation of MSC and CFSE-labeled PBMCs stimulated with PHA (2,5μg/ml) or rMOG (10μg/ml). The Index of MSC Suppression of myelin-activated memory T cells was calculated.

Results

In vitro, the inhibitory effect of MSC on myelin-induced $CD3^+CD45RO^+$ proliferation was more pronounced as compared to non-specific stimuli. Indices of MSC Suppression of $CD3^+CD45RO^+$ proliferation induced by PHA and rMOG made 26.1(16.3–44.3)% and 47.0(26.7–73.1)%, respectively, $p<0.01$. MSC capacity to suppress the myelin-induced proliferation correlated with *EDSS* ($R=-0.53$, $p<0.05$). *In vivo*, a significantly reduced *in vitro* myelin-stimulated T cells proliferation was identified 6–9 months after therapy mostly due to $CD4^+CD45RO^+$ lymphocytes suppression.

Conclusion

The Index of MSC Suppression may be a criterion for estimating MSC immunosuppressive potential. Intravenous MSC administration resulted in suppressed myelin-stimulated T cells proliferation during 9^{th}-12^{th} month after transplantation thus characterizing *in vivo* immunomodulatory effect of cell therapy in MS.

AUTO1-0322
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

CD4+CD25+FOXP3+ REGULATORY T CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: THE NEGATIVE ASSOCIATION WITH DISEASE ACTIVITY, ACUTE COURSE, TRANSITIONAL B CELLS AND IGG LEVELS

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Background

CD4+ CD25+ Foxp3+ regulatory T (Treg) cells play a key role in maintaining peripheral tolerance and preventing autoimmune diseases. Quantitative and/or qualitative deficiencies of Treg have been associated with immune disturbances in systemic lupus erythematosus (SLE).The main goal of the study was to determine the relationship of CD4+CD25+FoxP3+Treg cells with clinical and immunological manifestations in SLE patients (pts).

Method

Frequencies and absolute numbers of peripheral blood CD4+CD25+FoxP3+Treg cells were assessed in 21 healthy donors and 20 SLE pts (2012 SLICC classification criteria); (1M/19F); age 32±13 years; disease duration median (25–75 percentile) 5(1-10) years; SLEDAI2K≥10 - 15(10-22) (14 pts), <10 – 7(6-8) (6 pts). All pts were treated with prednisone, hydroxychloroquine, azathioprine, mycophenolate mofetil, cyclophosphamide. CD4+CD25+FoxP3+ Treg cells and B-cell subsets were analyzed using multicolor flow cytometry.

Results

Compared with healthy donors, SLE pts demonstrated significant lower the absolute number of Tregs (0.05; 0.04-0.06 vs 0.03;0.02-0.05x10^9/L, p<0,036), with a high percentage Treg (8.8;7.5-10.5 vs 12.0;8.8-17.0%, p<0.02). The median percentage of Tregs was lower in pts with acute SLE compared to chronic SLE pts (9.0;8.3-9.9 vs 13.5;12.7-18.7%, p<0,02). SLE pts with high activity had a lower frequencies of Tregs (10.2;8.5-15.0 vs 15.8;12.7-20.4%, r=-0,51, p<0,05). Low count of Tregs correlated with elevated level of IgG (r=-0,52, p<0,05). Absolute number of Tregs correlated negatively with percentage and absolute count of transitional (CD19+IgD+CD10+CD38++CD27-) B cells (r=-0,66 and r=-0,63, p<0,05).

Conclusion

Decreased amount of T regs in SLE is associated with high disease activity, acute course and expansion of autoreactive B cells.

AUTO1-0213
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

FLOW CYTOMETRIC DETERMINATION OF CD4+CD25+CD127LOW/NEG REGULATORY T CELLS AND MONOCYTE HLA-DR EXPRESSION IN PREDICTION OF EARLY IMMUNOSUPPRESSION - AN EXAMPLE OF ACUTE PANCREATITIS

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Background

Early detection of severe forms with adverse outcomes is the cornerstone that can provide a reduction in morbidity and mortality in acute pancreatitis (AP).
The aim of this study is the monitoring of immunosuppressive response in AP by flow cytometric determination of $CD4^+CD25^+CD127^{low/neg}$ regulatory T cells (Tregs) and monocyte HLA-DR expression (mHLA-DR) in peripheral blood and evaluation of their role as a prognostic markers.

Method

We analyzed 74 patients with AP, at admission, on the 48-th hour and on the 5-th day. In the study group 16(21.6%) patients were with severe AP (SAP), 19(25.7%) - with moderate AP (MoAP) and 39(52.7%) with mild AP (MAP).

Results

Patients with SAP had significantly higher percent of Tregs at admission and on the 5^{th} day than these in MoAP (p-0.007; p-0.033 respectively). The cut-off value in SAP prognosis was 8.75%, as measured at admission (AUC-,795). Patients with SAP had significantly lower mHLA-DR at admission than these with MoAP and MAP (mean SAP – 47.6% SD-12,5; mean MoAP – 51.1% SD- 12.5; mean MAP – 77.8% SD – 22.8) (p-0.005; p-0.000 respectively) with prognostic cut-off value 45.3% (AUC-.834). Patients with poor outcome had significantly lower levels of HLA-DR on the 5-th day (mean favorable outcome–70.5%, SD-16.5; mean unfavorable outcome-35%, SD-4.3; p-0.000), with prognostic cut-off values - 38% (AUC - .944).

Conclusion

The dynamic tracking of immunosuppressive response in AP by routine flow cytometric determination of Tregs and mHLA-DR could be associated with adequate disease evaluation and timely therapeutic decisions.

AUTO1-0373
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

CD63 MONOCLONAL ANTIBODY CLONE COS3A UP-REGULATES INTERLEUKIN-10 PRODUCTION OF MONOCYTES AND SUPPRESSES T CELL ACTIVATION

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Background

CD63, known as lysosomal associated membrane protein 3 (LAMP-3), is a member of the tetraspanin family proteins which is ubiquitously expressed by all leukocytes and is exerted in several cellular processes. This molecule is weakly expressed on T lymphocytes, but up-regulated during T cell activation, indicating the involvements in T cell response. However, only few studies about its role on T cell biology have been described.

Method

Effect of an in-house CD63 monoclonal antibody (mAb) clone COS3A on T cell proliferation and cytokine production was observed using peripheral blood mononuclear cells as a study model.

Results

The mAb COS3A inhibited CD3-mediated T cell proliferation. The inhibitory effect was associated with down regulation of IL-2 and its receptor (CD25) and IFN-γ of T cells. Alternatively, this mAb enhanced the production of IL-10, an anti-inflammatory cytokine that known as T cell proliferation suppression factor, by monocytes. Remarkably, the inhibitory effect of the mAb COS3A on cell proliferation was diminished by addition of anti-IL-10 mAb. Moreover, the inhibitory effect was dramatically reduced while monocytes and B cells were depleted.

Conclusion

These results conclude that the mAb COS3A suppressed T cell proliferation by increasing the IL-10 production of monocytes, which latter took part as T cell suppressor factor. Further studies are in progress to elucidate the actual role of the CD63 on T cell response.

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AUTO1-0295
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

THE EFFECT OF SPLENECTOMY ON B CELL SUBSETS.

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Background

The spleen is crucial in regulating of immune homoeostasis through its ability to link innate and adaptive immunity and in protecting against infections. Patients after splenectomy are susceptible to the risk of bacterial infections, hematological tumors, and controversial data exist about autoimmune diseases induction. The reduction of memory B cells have been reported. Aim of the study was B cells subsets analysis; mainly memory, naive, transient and plasmablasts subsets.

Method

B cells immunophenotyping: flow cytometry with CD19, CD27, CD38, IgM and IgD in the splenectomized patients suffering with hereditary spherocytosis (n=20), immune thrombocytopenic purpura (n=14), injury (n=75) and healthy controls (n=12).

Results

Reduction of $CD27^+$ memory B cells and more profoundly $CD27^+IgM$ cells was found in all splenectomised patients groups in comparison to healthy controls ($p<0,01$). These results have correlated with significantly increased levels of naive B cells in all patients groups ($p<0,01$). Higher proportions of plasmablasts (IgM^-CD38^{hi}) and transient B-cells (IgM^+CD38^{hi}) were found in all splenectomised patients group, despite the fact of the last vaccination (done more then one year ago).

Conclusion

Acquired data could affirm splenectomy is associated mainly with diminishing of IgM^+ marginal zone memory B cells. Possibly new findings: increase of transient B cells and plasmablasts in periphery without any relation to previous vaccination history. Our results could support idea of the fundamental importance of the spleen marginal zone in early phase of immune defense reaction and, further, expected decline of natural (auto)antibodies with its (potentially) protective effect againts autoimmune pathology induction.

AUTO1-0410
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

INCREASED PERCENTAGES OF TRANSITIONAL BREGS IS A CHARACTERISTIC FEATURE OF NATALIZUMAB-INDUCED REMISSION IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Background

Deficiency and functional impairment of Bregs is a characteristic feature of autoimmune disorders. However, their role in the induction and perpetuation of MS is uncertain as reported data describe increase, decrease or no effect in Breg status under treatment. Since Breg discrepancies arise primarily due to diverse therapeutic regimens and uneven/heterogenous patient cohorts, our aim was to investigate peripheral Breg homeostasis and functionality, in a well-defined RRMS patient cohort under natalizumab-induced remission.

Method

PBMCs were obtained from 24 RRMS patients (12 in remission under natalizumab, 12 at relapse under first or second line treatment) and 12 healthy controls (HC). Breg enumeration and their ability to secrete IL-10 was analyzed by flow cytometry using B cell specific IL-10 induction agonist (ODN2006-TLR-9) and fluorochrome conjugated monoclonal antibodies.

Results

The percentages of memory Bregs did not differ between relapsing (5.3±2.2) and remitting RRMS patients (7.7±4.2) or HCs (6.1±1.5). The percentages of transitional Bregs were significantly increased in remitting RRMS patients (1.7±0.5, n=12 compared to relapsing RRMS patients (0.6±0.4, $p<0.01$) and were comparable to HCs (1.85±0.5). Also, IL-10(+) Bregs were significantly increased during natalizumab-induced remission compared to relapsing RRMS and were enriched within CD19(+)CD24(hi)CD38(hi) transitional cell compartment.

Conclusion

Natalizumab-induced remission is accompanied by significant increase of regulatory B cells. Impaired Breg status may indicate potential relapses to treatment.

AUTO1-0378
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

FOLLICULAR HELPER T CELLS ARE EFFECTIVELY CONTROLLED BY BREG CELLS IN SJÖGREN'S PATIENTS BUT ARE NOT CONTROLLED IN SLE PATIENTS

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Background

Humoral immune response is dependent on follicular helper T (Tfh) cells. We recently showed that Regulatory B (Breg) cells from healthy controls inhibit the Tfh-dependent antibody secretion. Abnormal antibody production in autoimmune situations might thus result from defective Breg actions.

Method

In vitro autologous co-culture systems with T and B cells from pSS and SLE patients were developed to study 1- the polarization of human T cells into Tfh cells and 2- the Tfh-dependent terminal differentiation of B cells into antibody-secreting cells. Breg influences on this two-step humoral immune response were assessed.

Results

Stimulated by IL-12 and IL-21, pSS T cells polarized into Bcl-6high, IL-21+, ICOShigh, CXCR5high and PD-1high Tfh cells. These cells induced the terminal differentiation of naive pSS B cells into CD138+ plasma cells and IgD-CD27+ memory B cells, and triggered the secretion of immunoglobulins. TLR9-stimulated pSS Breg cells restrained the Tfh cell polarization, inhibited the Tfh-dependent terminal differentiation of B cells, and abrogated the associated secretion of immunoglobulins. Stimulated SLE T cells also differentiated into Tfh cells that induced the SLE B cells to differentiate into plasma and memory cells and triggered the secretion of immunoglobulins. However, SLE Breg cells were unable to control the Tfh cell polarization, to inhibit the Tfh-dependent B cell differentiation and to restrict the subsequent immunoglobulin productions.

Conclusion

The Tfh-dependent humoral response is efficiently controlled by the Breg cells in pSS but not in SLE patients suggesting that aberrant autoantibody production in both autoimmune situation results from distinct pathophysiological mechanisms.

AUTO1-0799
T CELLS AND B REGULATORY CELLS (TREG, BREG) - TOLERANCE

REGULATORY CELLS AND MOLECULES IN THE SKIN OF PSORIATIC PATIENTS

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Background

Psoriasis is one of the most disabling skin diseases, in which T cells play a major pathogenic role. Skin biopsies taken from psoriasis patients are heavily infiltrated with T cells, mainly pro-inflammatory such as CD4 and TH-17 T cells. These are the source of many pro-inflammatory cytokines, such as IL-12, IL-17 - targets of many therapeutic agents in this field. The status of local regulatory molecules and cells in psoriasis and other immune mediated skin diseases is still lacking. We therefore designed this study aiming to analyze the expression of CTLA-4 (a marker of T regulatory cells) and other regulatory molecules/cytokines, namely, neuropilin-1 (NP-1), semaphorin3A and IL-10 in psoriatic skin biopsies.

Method

Skin biopsies taken from 20 psoriatic patients and 10 normal skin biopsies were immune-stained for the expression of IL-10, IL-17 ,semaphorin3A/CTLA-4 and neuropilin-1/CTLA-4.

Results

The positive staining of semaphorin3A\CTLA4 and neuropilin-1\CTLA4 was significantly higher in normal skin compared to skin biopsies taken from psoriatic patients. In correlation with the above, the staining of IL-10 was significantly lower and IL17 was significantly higher in psoriatic skin compared to normal skin.

Conclusion

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These results suggest that T cell mediated skin inflammation in psoriasis is due to the lack of sufficient immune regulation. Future therapies should be directed aiming to correct/improve the above regulatory deficits.

AUTO1-0544
THYROID AUTOIMMUNITY

ATYPICAL COURSE OF AUTOIMMUNE THYROIDITIS

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Background

Chronic lymphocytic thyroiditis, traditionally named Hashimoto's disease, is caused by autoimmune processes. Typically, it is characterized by progressive thyroid destruction leading to a decrease of thyroid volume and hypothyroidism.
Herein, we present a case of atypical course of chronic lymphocytic thyroiditis.

Method

60 years old female was admitted to the endocrinology outpatient clinic due to the rapid thyroid enlargement with neck pain and dysphagia. Complaints lasted for 2 weeks. The patient had a 20 years history of autoimmune thyroiditis, initially with hyperthyroidism then hypothyroidism treated successfully with l-thyroxine.

Results

Clinical examination revealed enlarged, though thyroid gland without any palpable nodules. No lymph nodes in the thyroid area were found. Ultrasound examination showed an increase in total thyroid volume (34,5 ml vs. standard volume < 18 ml). To exclude anaplastic carcinoma or thyroid lymphoma, diseases with rapid thyroid growth, fine needle biopsy was recommended. Features of chronic lymphocytic thyroiditis were found with no signs of neoplastic process. Prednisone in an oral dose of 20 mg daily was given for 3 months. This treatment resulted in symptoms relief as dysphagia disappeared, thyroid became smaller in size and painless. Palpably, the gland was much softer than before steroid administration. Furthermore, ultrasound examination showed a reduction in thyroid volume (28 milliliters). The glucocorticoids were gradually withdrawn. The patient needs further observation with medical controls recommended every 4 weeks.

Conclusion

We conclude that common autoimmune thyroiditis may have atypical course. Differential diagnosis is highly recommended.

AUTO1-0422
THYROID AUTOIMMUNITY

COMPARISON OF FOUR IMMUNOASSAYS AND ONE BIOASSAY FOR THEIR ABILITY TO DIAGNOSE GRAVES' DISEASE

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Background

Graves' disease (GD) is characterized by the presence of stimulatory anti-TSH receptor autoantibodies leading to hyperthyroidism and uncontrolled thyroid hormone synthesis. Here, we assess the performance of four anti-TSH receptor antibodies immunoassays and one cAMP-bioassay for the diagnosis of Graves' disease.

Method

in this observational study we retrospectively analyzed 122 serum samples of patients presenting with GD and 48 diseased controls (16 Hashimoto's disease, 9 thyroiditis, 13 thyroid autonomy, 10 other). Analysis was performed by BRAHMS TRAK human KRYPTOR (Thermo Fisher Scientific), RSR Fast TRAb ELISA (RSR Limited), IMMULITE 2000 TSI (Siemens Healthineers), EliA anti-TSH-R (Thermo Fisher Scientific) and stimulatory/inhibitory cAMP bioassays (RSR Limited).

Results

ROC curve analysis of the assays revealed AUCs between 0.905 and 0.957 resulting in a diagnostic sensitivity and specificity ranging from 77.9% to 94.3% and 87.2% - 93.7% respectively at cutoffs defined by the manufacturer

Conclusion

Third-generation immunoassays are suitable for the diagnosis of GD. In our hands the cumbersome bioassay showed the lowest sensitivity and specificity, whereas immunoassays performed similarly.

AUTO1-0732
THYROID AUTOIMMUNITY

ANALYSIS OF ZINC TRANSPORTER ZnT8 AUTOANTIBODIES IN CHILDREN AND ADOLESCENTS WITH AUTOIMMUNE THYROID DISEASES AND DIABETES TYPE 1

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Background

Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. It was demonstrated that ZnT family plays an important role in the synthesis and secretion of many hormones.

Method

The study was performed in the group consisting of 44 Graves' disease (GD) patients, 66 Hashimoto's thyroiditis (HT) patients, 166 patients with T1DM and 58 healthy controls. GAD, IA-2, IAA, ZnT8, 21OH antibodies' concentration were evaluated in the peripheral blood.

Results

ZnT8 Ab was found in 4 patients (9.1%) with GD while 4 patients (9.1%) were positive for GAD Ab, two patients (4.5%) were positive for IA-2 Ab and one patient (2.2%) was positive for IAA. Of these, one GD patient was positive for all four diabetes associated antibodies and one was positive for GAD Ab and ZnT8 Ab, two GD patients (4.5%) were positive for ZnT8 Ab only. In the case of HT patients, 6 (9.1%) were positive for ZnT8 Ab, while 4 patients (6.1%) were positive for GAD Ab, 4 (6.1%) were positive for IA-2 Ab and 3 (4.5%) were positive for IAA Ab. Of these, one HT patient was positive for all four diabetes associated antibodies, 2 had 3 diabetes associated antibodies (ZnT8 Ab,IA-2 Ab, GAD Ab or IAA) and one had 2 diabetes associated antibodies (GAD Ab and IAA), 3 HT patients (4.5%) were positive for ZnT8 Ab only.

Conclusion

These results show the presence of ZnT8 autoantibodies not only in patients with DT1 but also with AITD.

AUTO1-0456
THYROID AUTOIMMUNITY

"QUALITY OF LIFE AND NEUROPSYCHIATRIC DISORDERS IN PATIENTS WITH GRAVES' ORBITOPATHY: CURRENT CONCEPTS"

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Background

Graves' disease (GD) is an autoimmune chronic thyroiditis frequently associated with development of Graves' orbitopathy (GO) characterized by proptosis, strabismus, impairment of visual function, ocular surface inflammation and dry eye. As consequence, patients with GO experience impairment of quality of life and social function and could develop a neurobehavioral syndrome, ranging from anxious to depressive or psychotic disorders.

Method

Relevant studies were identified through a systematic literature search using the PubMed. No cut-offs regarding dates were imposed. We used the terms "Graves' Disease" or "orbitopathy", "ophthalmopathy", "psychosocial function", "neuropsichiatry disease" and "quality of life". Articles in English, French, German, Croatian, Spanish, and Italian were eligible for inclusion.

Results

To date, the pathogenic mechanism underlying neuropsychiatric disorders in patients with GD has not been clearly understood. In fact, the development of neuropsychiatric disorders in patients with GO has been associated with both the detrimental effects of the altered circulating thyroid hormones on the nervous system, and with the psychological discomfort caused by poor quality of life, reduced social interactions and relapsing course of the disease.

Conclusion

We summarize current evidence on neuropsychiatric abnormalities in Graves' disease focusing on its impact on QoL and psychosocial function. We remark the importance of a multidisciplinary approach and we emphasize the potential benefit of neuropsychiatric approach on disease perception, patient compliance to medical and/or surgical treatment and clinical outcomes.

AUTO1-0674
THYROID AUTOIMMUNITY

CLINICAL RESPONSE TO TOCILIZUMAB IN A WOMEN WITH SEVERE THYROID EYE DISEASE.

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Background

Graves' orbitopathy is the extrathyroidal manifestation of Graves' disease, which is the most common cause of exophthalmos. Tocilizumab has been suggested to be an effective therapy for moderate to severe thyroid eye disease. We describe the clinical response of a women with severe Graves' Disease refractory to intravenous steroids.

Method

Clinical and laboratory follow-up. Tocilizumab Protocol: 6 doses of IV Tocilizumab. Dose: 500 mg with a 30 days interval between doses. Follow-up: 6 months.

Results

A 49 year old white women had a clinical history of obstetric antiphospholipid syndrome (High titer IgM anticardiolipin and anti-beta-2 glycoprotein-I antibodies and fetal death). She associated C3 and C4 hypocomplementemia. During follow up she developed signs and symptoms of Graves's Disease with progressive severe ophthalmopathy. Anti-TSH receptor antibodies were positive. Several doses of high dose steroids was used with no significant and maintained response. Compassionate use of Tocilizumab was accepted by the patient. The patient demonstrated a progressive improved clinical activity score with no side effects after Tocilizumab therapy. Anti-TSH receptor antibodies decreased from 11.7 IU/L to 4.6 IU/L during the first month of therapy. Intraocular pressure was 18 mmHg in both eyes.

Conclusion

Tocilizumab was well tolerated and associated with a good clinical response in a women with Graves' Ophthalmopathy after therapy with this monoclonal antibody against IL6-receptor.

AUTO1-0741
THYROID AUTOIMMUNITY

CONFLICT OF VARIOUS AUTOIMMUNE EFFECTORS IN HASHIMOTO'S THYROIDITIS

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Background

Because of physiologic autoimmunity phenomenon and due to possible reciprocal effects of various autoantibodies (AB), the diagnostic significance of certain AB in disease may be equivocal. Hence, registration of their specificity by immunological methods sometimes does not give any information on their stimulatory or blocking action. An example is Hashimoto's autoimmune thyroiditis (AIT). AB in autoimmunopathies often cause damage to their targets diminishing their function. However, AIT is paradoxical: Hypothyroidism in it can unexpectedly transform into hashitoxicosis and vice versa. Parallel processes of immune mediated destruction and cytostimulation by anti-TSH-receptor (R-TSH) AB may cause it.

Method

We studied content of AB to thyroglobulin (TG), thyroperoxidase (TPO) or R-TSH, and levels of cortisol, prolactin and vitamin D_3 by ELISA in 102 AIT patients (89 females) from 4 to 80 years old, with various thyroid function.

Results

96.5% were positive for AB to TG either TPO, the last were detected twice more often. AB to R-TSH (from traces to 156 IU/l) revealed in 96.1% of cases. The level of vitamin D_3 in AIT was low (27.13±0.08 ng/ml), compared to reference values (30 ng/ml). Systemic hormonal parameters – prolactin and cortisol – affected the course of antithyroid autoimmunity in opposite ways. In hashitoxicosis (17 cases), higher level of prolactin was detected ($p < 0.001$).

Conclusion

Although higher levels of AB to TPO observed in hypothyroid cases, general spectrum of AB poorly correlated to thyroid function, presumably due to variation in possible thyroid stimulating or blocking reciprocal effects of AB to R-TSH, not detectable by ELISA.

AUTO1-1021
TYPE 1 DIABETES MELLITUS

BIOMARKERS OF AUTOIMMUNE DISEASES AND GENDER: APPROPIATENESS AND ASSOCIATION IN LADA (DIABETES AUTOIMMUNE LATENTE OF THE ADULT)

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Background

LADA is characterized by insulin resistance; autoantibodies to pancreatic insula (ICA), anti-tyrosine phosphatase autoantibodies (IA-2) and anti-decarboxylase autoantibodies of glutamic acid (GADA). The cut offs for the diagnosis of LADA are: presence of antibodies (GADA; IA-2), age> 35 years, insulin independence for at least 6 months from diagnosis. An association between LADA and M.A.R.I.C.A. for a diagnostic profile, disaggregated by gender, for an early diagnosis of LADA.

Method

Of 144 patients, 40 healthy donors and 94 patients (65 females and 29 males) classified according to the criteria of the ACR (American College of Rheumatology). Glycemia, ANA, ICA, anti-IA-2 and anti-GAD antibodies were tested.

Results

7% of the samples were positive for anti-IA-2 antibodies (p-value <0.0001, OR> 1); 5% anti-GAD antibodies (p-value <0.0001, OR> 1); while 3% ICA antibodies (p-value = 0.3, OR <1). Of the anti-positive IA-2 71% are females (p-value = 0.01) and 23% males (p-value = 0.01) while for anti-GAD 100% are females (p-value = 0.01), for the ICA 75% are females and 25% are males (p-value = 0.3). An association of ANAs with speckled pattern (s) was found in samples positive for anti-IA-2 (40%); for anti-GAD (57%) and ICA (60%) with p-value = 0.03.

Conclusion

The anti-GAD and anti-IA-2 antibodies have high significance and diagnostic accuracy especially in the female gender; there is an association between ANA and LADA in the female gender for a diagnostic profile disaggregated by gender in patients with LADA and with suspicion MARICA for precision and personalized medicine.

AUTO1-0043
TYPE 1 DIABETES MELLITUS

COMPARISON OF NATURAL KILLER CELLS AND THE OCCURENCE OF BETA CELLS AUTOANTIBODY IN SIBLINGS OF PATIENTS WITH TYPE 1 DIABETES MELLITUS TO HEALTHY CHILDREN

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Background

NK cells from patients with type 1 diabetes (DM1) have numeric and functional abnormalities. However, little is known about NK cells in healthy siblings of children with DM1.The aim of the study is to compare the number of NK cells and the correlation between NK cells and beta cells autoantibody in healthy siblings of children with DM1 to healthy children from non-diabetic families and to children with DM1.

Method

Peripheral blood mononuclear blood cells were obtained from 78 children with DM1, their siblings - 102, and 30 healthy children. NK cells were characterized by flow cytometry FACSCalibur (Becton Dickinson, USA). The auto-antibodies were determined by ELISA.

Results

The number of NK from the siblings was lower (average percentage 11,93±5,62) than that in the control group of healthy children (14,89±7,78) (p=0,02). There was no significant difference in the number of NK cells between children with DM1 and their siblings (p=0,11).

The levels of anti IA2 antibodies and anti ZnT8 Ab were statistically significant higher in siblings in comparison to the control group of healthy children (anti IA2 Ab p=0,0000001; anti ZnT8 Ab p=0,00001). The level of anti-GAD in siblings was similar to that in the control group. There was a positive correlation between the reduced number of NK cells and the co-occurrence of anti-GAD and anti ZnT8 Ab (the May-Whitney test Z=-2,02; p=0,04) in the diabetic patients.

Conclusion

The results suggest that the dysfunction of NK cells contributes to the autoimmune pathogenesis of type 1 diabetes and is connected with genetic predisposition to DM1.

AUTO1-0885
TYPE 1 DIABETES MELLITUS

COUMARIN-GLYCOSIDES FROM HYDRANGEA PANICULATA, SLOW DOWN THE PROGRESSION OF DIABETIC NEPHROPATHY BY TARGETING TGFβ1-SMAD AND Nrf2

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Background

Water extract from *Hydrangea paniculata* (HP), rich of coumarin glycosides, has been demonstrated to have renal protective effect on LPS-induced acute kidney injury by anti-inflammation and anti-oxidation. However, whether it also has beneficial effect on diabetic nephropathy is not clear.

Method

In the present study, the type 1 diabetes animal model was established by intraperitoneal injection of streptozotocin. HP was orally administrated every day for total three month. Biochemical analysis and histopathological staining were conducted to evaluate the renal functions. Pharmacokinetics in vivo was conducted to analyze the metabolites of HP with high blood drug concentration. In vitro study with these metabolites to analyze its protective mechanism on diabetic nephropathy.

Results

During the treatment, HP significantly reduced blood urea nitrogen (BUN), serum creatinine (Scr), and urine albumin excretion in diabetic rats, and increased the creatinine clearance rate (Ccr). By PAS staining, HP also ameliorated the glomerulosclerosis and tubular vacuolar degeneration. By pharmacokinetics study, the major coumarin compounds from HP were metabolized into umbelliferone and esculetin, which had high blood drug concentration with skimmin. By *in vitro* test, umbelliferone and esculetin has been demonstrated to significantly increase the mRNA level and protein level of nuclear factor (erythroid-derived 2)-like 2 (NRF2), down-regulate fibronectin and collagen IV of HK2 cells stimulated by TGFβ1, and TGF-smad signaling pathway was also inhibited.

Conclusion

HP has beneficial effect on diabetic nephropathy via increasing NRF2 expression and inhibit the TGF-smad signaling.

AUTO1-0745
VASCULITIDES, HORMONES AND AUTOIMMUNITY

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: ABOUT 11 CASES

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Background

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small- and medium-vessel necrotizing vasculitis, characterized by extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils occuring in patients with adult-onset and severe asthma. Antineutrophil cytoplasmic antibodies (ANCA) are present in about 40 % of patients.

Method

It's a multicentric descriptive and retrospective study relating the cases of EGPA diagnosed and monitored in the center of Tunisia between 2000 and 2017.

Results

Eleven patients were analyzed (4 men and 7 women). Mean age at onset was 45 years. Asthma preceded the vasculitis with a Median time of 3 years.

The main clinical manifestations at diagnosis was skin's lesions, pleuropulmonary and neurological manifestations noted respectively in 81, 90, and 72 % of the cases. An abnormally high level of eosinophils was constantly noted. Positivity of ANCA was found in 4 patients (36 %).

Corticosteroid therapy was administered as induction treatment in 10 patients on average of 6 weeks. In 8 cases, it was initiated by intravenous bolus of methylprednisolone. Cyclophosphamide was used as induction treatment, in combination with steroids in 5 patients with an FFS of 1.
3 patients were treated with azathioprine as maintenance treatment after 6 bolus of cyclophosphamide.

Complete remission was obtained in 6 patients including a late one. Relapse occurred in 3 patients. The total number of relapses was 5 including 4 minor ones one and a major one.

Conclusion

EGPA is also rare in our country but our study doesn't identify any epidemiological, clinical or evolutive particuliarities of the EGPA in Tunisia

AUTO1-0746
VASCULITIDES, HORMONES AND AUTOIMMUNITY

NECROSIS OF THE TONGUE, AN UNUSUAL WAY OF REVEALING GIANT CELL ARTERITIS'S DISEASE

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Background

Giant Cell Arteritis is a systemic vasculitis of unknown cause,which concerns the aorta with predilection of involvement of the branches of the external carotid artery.Ischemic manifestations are possible nevertheless the necrosis of the tongue is exceptional

Method

We report a case of which necrosis of the tongue revealed Giant cell disease

Results

An 81-year-old patient,without pathological history,presented with necrosis of the tongue.We found continuous holocranial headaches history since 2 months,resistant to analgesics,asthenia,unmeasured weight loss added to inflammatory polyarthralgia of both shoulders,without fever or visual disturbances.Three weeks earlier,the patient described tongue pain associated with edema and difficulty when speaking and swallowing.On physical examination,the patient had an enlarged tongue with a blackish appearance of the outer extremity to half of the tongue.The temporal pulse was abolished on the left.Ophthalmological examination was normal.On biology,we noted an inflammatory syndrome:the sedimentation rate at 50,CRP at 66mg/l,white blood cells at 15000 / mm3,and an inflammatory profile in the electrophoresis of proteins,the ANCA were negative.Despite the negativity of the biopsy of the temporal artery and the biopsy of the tongue, the strong suspicion of Giant cell arteritis disease led us to prescribe steroids at the dose of 1 mg/kg/day with a good clinical course marked by regression of the headache,the joints manifestations,general signs,with restitution ad integrum of the tongue.

Conclusion

Lingual necrosis is rare and giant cell arteritis disease is not the only etiology.The differential diagnosis is discussed with malignancies, infections and drug intake.It is necessary to eliminate them to retain the diagnosis especially if the clinical presentation is atypical.

AUTO1-0355
VASCULITIDES, HORMONES AND AUTOIMMUNITY

HISTOPATHOLOGIC PREDICTORS OF OUTCOMES IN ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

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Background

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is the most common cause of rapid progressive glomerulonephritis (RPGN). Its prognosis has improved, but long-term patient morbidity and mortality still remains relatively high. The search for optimal predictors of long-term outcome of this disease is of particular importance.

Method

Retrospective study included one hundred fifteen biopsy-tested AAV-RPGN patients aged 56±14.3 years. According to histopathology the patients were divided into 4 groups: focal (n=22), crescentic (n=34), sclerotic (n=33), mixed (n=29) RPGN. Induction therapy consisted of methylprednisolone and cyclophosphamide IV pulses followed by oral prednisolone. Rituximab was used in 21 patients. Maintenance therapy consisted of prednisolone and azathioprine or MMF.

Results

Improvement observed in 77% of patients: 100%, 80%, 57% and 25% at focal, mixed, crescentic and sclerotic RPGN ($p<0,01$). Five-years patients survival rate was 67.7% and did not depend on the type of histomorphologic glomerular changes. It was decreased to 38% in patients older than 60 versus 81% in the younger group ($p<0,05$) and to 60% at dialysis-dependent renal failure in the onset of the disease ($p=0.03$).

Five-years renal survival equaled 59% and did not depend on the age of patients, the initial state of kidney function and the need for HD in the debut of the disease. Renal survival correlated with the histomorphological type RPGN: 89%. 78%, 56% and 34% in focal, mixed, crescentic and sclerotic type ($p<0.01$).

Conclusion

Our results show that histopathologic lesions of glomerular in AAV-RPGN has predictive value for renal outcome. Patient survival rate depend on the age and dialysis-dependent renal failure.

AUTO1-0824
VASCULITIDES, HORMONES AND AUTOIMMUNITY

SYSTEMIC VASCULITIS - A DIAGNOSTIC CHALLENGE

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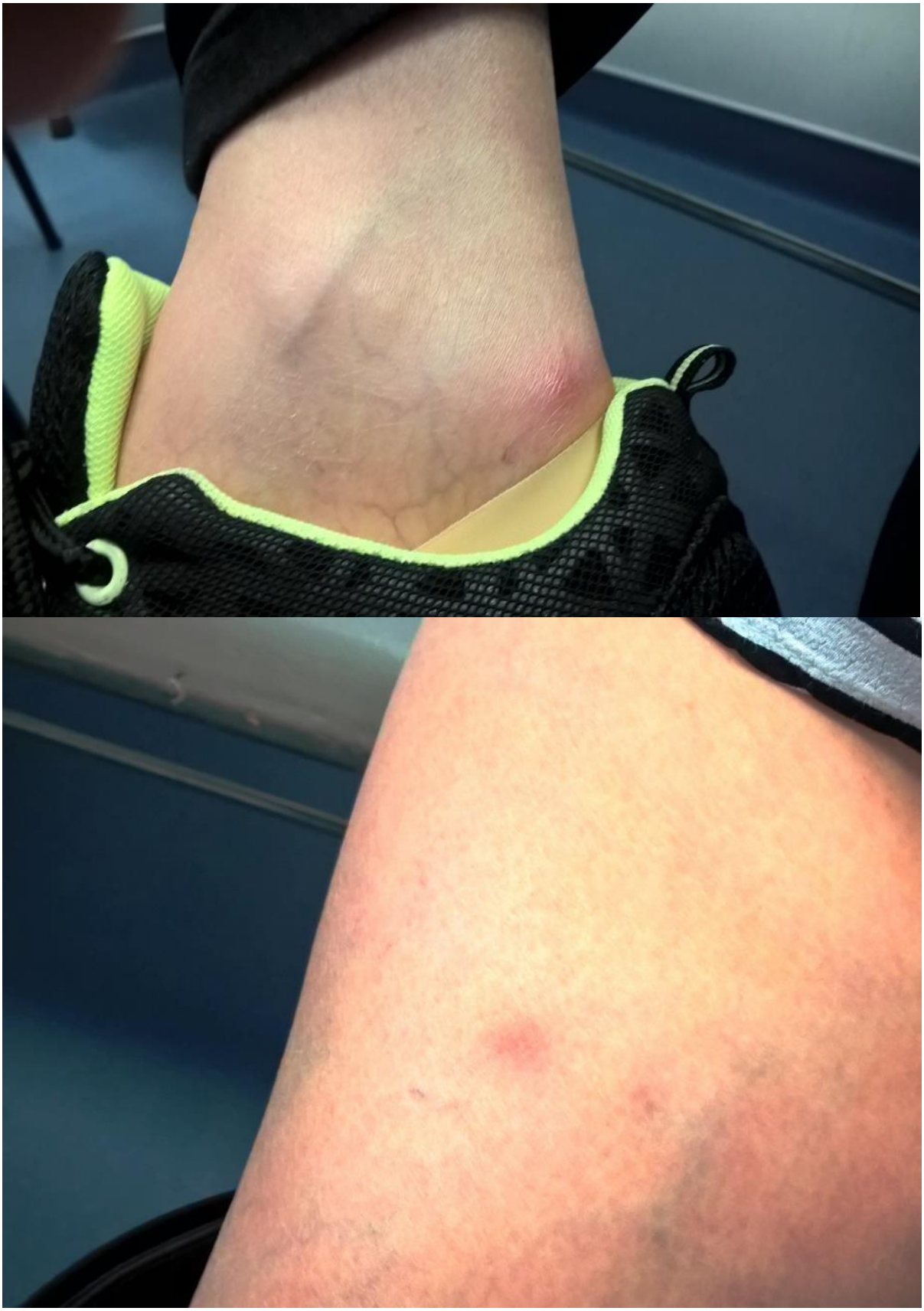
Background

Systemic vasculitis comprise a group of complex disorders involving blood vessels of varying size. It can be primary or secondary to a wide range of aetiologies. Clinical manifestations are diverse and may be non-specific, which difficulties the diagnosis. The distinction among the different vasculitides is not always easy despite the many classifications systems existent.

Method

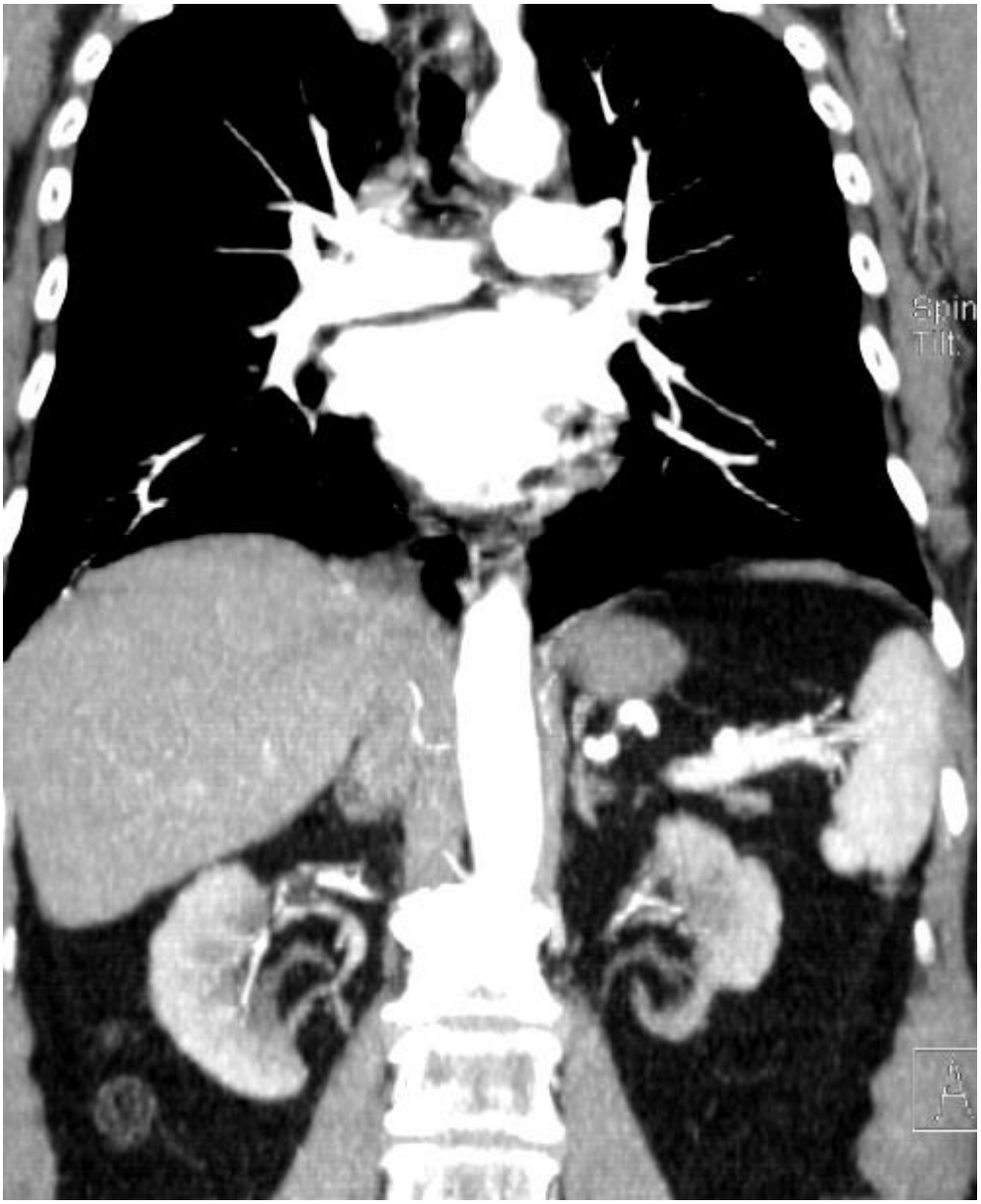
We present a 58-year-old woman, with an history of acute myocardial infarction, hypertension and chronic renal disease presenting with dry cough, fever, dyspnea and nodular lesions in the inferior limbs (Figure 1 and 2).



Results

The autoimmunity studies were negative to antinuclear antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, myeloperoxidase, proteinase 3 markers and anti-glomerular basement membrane antibodies. Malignancy was excluded. The sedimentation rate was high. The nodular lesions biopsy revealed alterations compatible

with medium vessels vasculopathy and systemic vasculitis. The renal angiotomography revealed atrophic kidneys and alterations compatibles with vasculitis, aneurysms were not seen (Figure 3). The electromyography was normal.



Conclusion

We do not have a definitive diagnosis. The main suspect is Polyarteritis nodosa, however, we can not exclude other causes of medium vessels vasculitis.

The patient was treated with glucocorticoids with resolution of the nodular lesions and improvement of the renal condition. Sometimes the patient takes the initiative to reduce the glucocorticoids which leads to a restart of the symptoms.

Our aim is to highlight the differential diagnosis of medium vessels vasculitis and the difficulty to make a final diagnosis. Many patients does not have a linear presentation and don't fulfill all the criteria presented in the classifications system.

AUTO1-0609
VASCULITIDES, HORMONES AND AUTOIMMUNITY

BEHCET'S DISEASE: NEW INSIGHTS INTO PATHOPHYSIOLOGY, CLINICAL FEATURES AND TREATMENT OPTIONS

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Background

Behçet's disease (BD) is a rare systemic vasculitis characterized by oral aphthous ulcers, genital ulcers, ocular lesions and other systemic manifestations. BD occurs most frequently in Eurasian populations along the ancient trading route known as the "Silk Road" which extends from eastern Asia to the Mediterranean basin.

Method

We performed a systemic review of the literature on Behçet's disease in the main scientific databases (Scopus, Pubmed, Web of Science).

Results

The causes of BD are unknown: it is believed to be due to an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals. HLA-B51 allele has been the most strongly associated risk factor for BD. Herpes simplex virus-1 and Streptococcus have been postulated as possible environmental triggers of BD. T cell homeostasis perturbation is supposed to be the cornerstone of BD pathogenesis. The histology shows vasculitis that involves vessels of any size. The diagnosis of BD is only supported by clinical criteria and require the exclusion of other diagnoses based on clinical presentation. There are no pathognomonic laboratorial findings of BD.

Conclusion

As there are no laboratorial findings of BD, the diagnosis is only supported by clinical criteria. Although the etiology of BD is still obscure the close correlation between the genetic internal and triggering external factors is thought to be present in the pathogenesis of BD. The recent progress in the knowledge of BD pathogenesis may pave the way for innovative therapy. There is the need of further studies to determine efficacy of different therapeutic options in BD.

AUTO1-0200
VASCULITIDES, HORMONES AND AUTOIMMUNITY

MYCOPHENOLATE MOFETIL AND HYDROXYCHLOROQUINE AS GLUCOCORTICOID-SPARING AGENTS IN POLYARTERITIS NODOSA: A CASE REPORT

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Background

Polyarteritis nodosa is a rare vasculitis that can be progressive and fatal. Early recognition and effective treatments are needed to improve its prognosis.

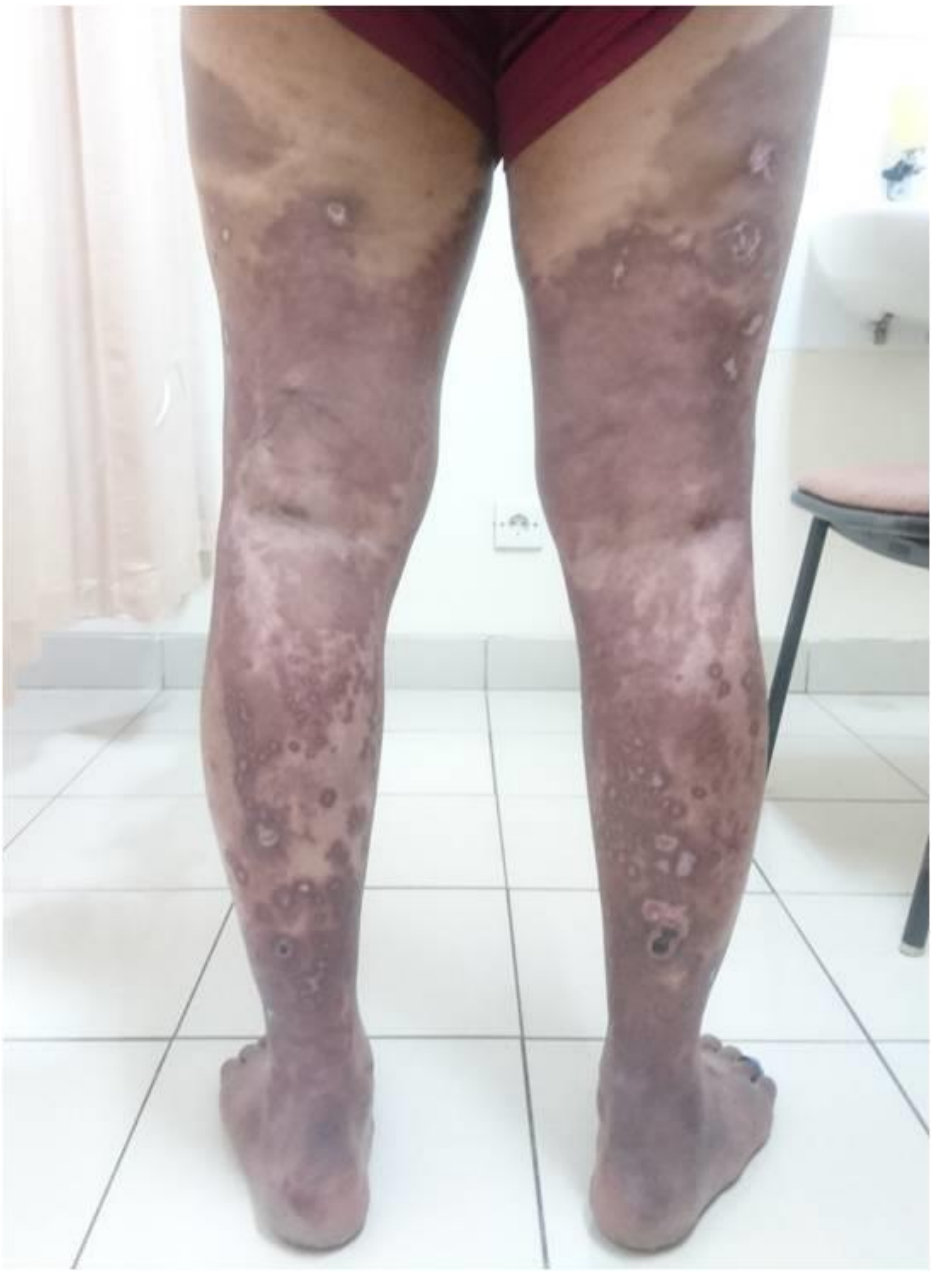
Method

Case

A 34-year old patient presented with tender purpuric lesions and livedo reticularis of the limbs for 6 months. Skin lesions began as erythematous patches spreading to the proximal of limbs and intermittently developed into painful violaceous ulceration. He had been diagnosed as hypertension, dyslipidemia, heart failure, stenosis of the right coronary artery, dilated cardiomyopathy, and recurrent abdominal pain since 3 years before. Complete blood count, urine analysis, and blood chemistry were normal. Anti-nuclear antibody test was positive (1:100). Other immunologic tests (ANCA, C3, C4, dsDNA, IgA, RF) were normal. Serologic tests for hepatitis, HIV, and gonorrhea were also negative. His vitamin D25-OH level was low (9.5 µg/dL). His CT angiography showed a narrowed left internal iliac artery. Skin biopsies showed necrotizing leukocytoclastic vasculitis with fibrinoid necrosis. He was treated with methylprednisolone (125 mg/day for 3 days then tapered), MMF (1 gram/day), hydroxycholoroquine (200 mg/day), vitamin D3 (2000 IU/day), dabigatran (150 mg, twice a day).After 2 months, the lesion improved

gradually and methylprednisolone is now tapered slowly.

Results



Discussion

Based on the ACR classification criteria, this patient was diagnosed as idiopathic PAN. Glucocorticoid with MMF had been used to treat PAN successfully in some reports. Hydroxychloroquine has anti-thrombotic, lipid-lowering, and glucose-lowering effects that might give additional benefits in patients with other co-morbidities.

.**Conclusion**

Combination of MMF, hydroxychloroquine, and glucocorticoid could be used in the management of PAN.

AUTO1-0802
VASCULITIDES, HORMONES AND AUTOIMMUNITY

METHOD COMPARISON OF AESKUSLIDES ANCA FOR THE DIAGNOSIS OF ANCA-ASSOCIATED VASCULITIS

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Background

AESKUSLIDES ANCA is an indirect immunofluorescence assay used to detect anti-neutrophil cytoplasmic autoantibodies (ANCA) in human serum. This in vitro diagnostic assay is used as an aid for the diagnosis of ANCA-associated vasculitis (AAV) in conjunction with other clinical and laboratory findings.

Method

A method comparison of ethanol and formalin fixed granulocytes was carried out between AESKUSLIDES ANCA (AESKU.Diagnostics) and the NOVA Lite ANCA of INOVA. 507 clinical serum samples (comprising 135 serum samples from patients with AAV and 375 samples from patients with other diseases) were analyzed by standard IFA protocols. Results were obtained by manual processing and reading.

Results

In this cohort, AESKUSLIDES ANCA Ethanol slides show higher sensitivities (48.5% vs. 36.4%) and specificities (69.3% vs. 55.2%) compared to INOVA. AESKUSLIDES ANCA Formalin slides show higher sensitivities (50.0% vs. 37.9%) and similar specificities (90.7% vs 91.5%) compared to INOVA.

Conclusion

AESKUSLIDES ANCA Ethanol showed higher diagnostic sensitivity (48.5%) and specificity (69.3%) compared to the predicate assay NOVA Lite provided by INOVA (36.4%, 55.2%). This is due to the fact, that AESKU assay detects more positives in the AAV cohort, and less positives in the other disease groups. AESKUSLIDES ANCA Formalin showed a diagnostic sensitivity (50.0%) compared to the predicate assay NOVA Lite provided by INOVA (37.9%). However, the diagnostic sensitivity was comparable between the two (90.7% vs 91.5%).

AUTO1-0754
VASCULITIDES, HORMONES AND AUTOIMMUNITY

RELAPSING POLYCHONDRITIS AND RHEUMATOID ARTHRITIS: ONE OR TWO SEPARATE DISEASES?

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Background

Relapsing polychondritis (RP) is a rare systemic inflammatory disease characterized by reccurent episodes of inflammation and destruction of cartilaginous structures in different organs (1). In approximately 30% of cases RP is associated with another autoimmune disease (1). We describe a patient with RP who developed seropositive rheumatoid arthritis (RA) after 5 years of follow- up.

Method

Method and Results

Results

A 56-year-old male patient was admitted to hospital because of high fever (39C) with a swollen, red and painfull left auricula, nose tip and redness of his left eye. He also had left-sided hearing loss, painful and erythematous ear canal and a painful left ankle joint. On admission laboratory findings showed leukocytosis and elevated inflammatory markers. Since broad spectrum antibiotic therapy was not efficient, prednisone (1 mg / kg/day) was introduced which led to rapid improvement. Based on positive 4/6 clinical criteria according to McAdams clasiffication (2) and rapid response to glucocorticoids according do Damiani/Levine criteria (3) he was diagnosed with RP. After 5 years of follow-up the patient developed seropositive rheumatoid arthritis with symetrical erosive arthritis, positive rheumatoid factor and HLA DR4. We continued prednisone with addition of methotrexate and achieved remission of both rheumatoid arthritis and RP.

Conclusion

In patients with RP there is a need for long term follow up and screening for associated rheumatoid arthritis or other autoimmune diseases.

AUTO1-1059
VASCULITIDES, HORMONES AND AUTOIMMUNITY

POLYARTERITIS NODOSA AND RHEUMATOID ARTHRITIS – A PROBABLY MORE THAN COINCIDENTAL ASSOCIATION

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Background

Polyarteritis nodosa(PAN) is a rare systemic vasculitis characterized by necrotizing inflammatory lesions affecting medium and small muscular arteries, resulting in microaneurysm formation and thrombosis.PAN is a multisystem disease, although most commonly affects skin, joints, peripheral nerves, gut and kidney.In rheumatoid arthritis (RA) clinically apparent vasculitis occurs in 1-8% of cases, which is typically described as a PAN-type vasculitis.Also, 15-70% of RA cases have vasculitis-associated neuropathy multiplex.

Method

Results

A 44-year-old woman presented with incapacitating myalgia and arthralgia on both legs with tender, subcutaneous nodules with a background of livedo reticularis (LR).Apart from fatigue, and 7Kg weight loss in 3month, she had no other symptoms.Physical examination was notable for bilateral maleolar hyperesthesia and distal LR. Analitically with normochromic normocytic anemia, leukocytosis and elevated erythrocyte sedimentation rate;pANCA and hepatitis serologies were negative.Renal arteriography showed microaneurysms and electromyography and skin biopsy,mononeuritis multiplex and neutrophilic vasculitis, respectively, confirming PAN diagnosis. Patient began glucocorticoids and cyclophosphamide treatment, that completely resolved PAN without sequelae.Five years later, she reported 1hour morning stiffness and bilateral arthritis involving the proximal interphalangeal,metacarpophalangeal and wrists. Rheumatoid factor and anti-CCP antibodies were positive and her hands X-rays had rheumatoid arthritis typical features.DMARDs treatment was promptly initiated and she presently achieved remission.

Conclusion

Vasculitis is considered a primary event in PAN but is also recognized in RA, where it has heterogeneous clinical presentation. Considering the prominence of immune components in these diseases and the similar pathologic changes in involved blood vessels, an autoimmune shared process must be considered in order to provide early recognition and treatment.

AUTO1-0259
VASCULITIDES, HORMONES AND AUTOIMMUNITY

CLINICAL CHARACTERISTICS OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY POSITIVE PATIENTS ASSOCIATED WITH LARGE VESSEL VASCULITIS

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Background

Antineutrophil cytoplasmic antibody (ANCA) is a diagnostic marker of small vessel vasculitis. However, ANCA is sometimes tested positive in patients with large vessel vasculitis. In this study, we investigated the clinical characteristics of ANCA positive patients with large vessel vasculitis.

Method

We retrospectively selected patients with ANCA positive large vessel vasculitis from the medical charts. We collected the data on clinical background, clinical diagnoses, and distribution of large vessel involvement.

Results

We found five ANCA positive patients with large vessel vasculitis. Three patients were MPO-ANCA positive and two were PR3-ANCA positive. Three of five patients were male and two were female. Age ranged from 38 to 86 years old. The clinical diagnoses included Takayasu arteritis in two patients and possible giant cell arteritis in one patient in MPO-ANCA positive patients, and possible granulomatosis with polyangiitis and relapsing polychondritis with ulcerative colitis in PR3-ANCA positive patients. In five patients, imaging studies showed that the cervical branches of aorta were involved in two patients, thoracic aorta in two patients, and abdominal aorta and its branches in one patient. In the patient with possible giant cell arteritis, the diagnosis was based on clinical findings, and the inflammation of temporal artery was not apparent on biopsy specimen.

Conclusion

Although rare, ANCA was positive in patients with large vessel vasculitis. The significance and pathogenesis of ANCA in large vessel vasculitis remains controversial, but the screening for large vessel involvement may be recommended in ANCA positive patients if they do not show small vessel involvement.

AUTO1-1061
VASCULITIDES, HORMONES AND AUTOIMMUNITY

SUBGLOTIC TRACHEAL STENOSIS IN GRANULOMATOSIS WITH POLYANGIITIS

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Background

Granulomatosis with polyangiitis (GPA) is a rare multisystem autoimmune disease, which predominantly affects the upper and lower respiratory tracts and the kidneys. It's characterized by necrotizing granulomatous inflammation and pauci-immune vasculitis in small and medium-sized blood vessels. Subglotic tracheal stenosis can be found in 16 to 23% of these patients.

Method

We reviewed a case of GPA with subglotic tracheal stenosis.

Results

We present the case of a 79-year-old woman with the diagnosis of GPA in remission over two years, on azathioprine and low dose prednisolone, admitted with cough, dyspnea, wheezing and stridor, without improvement with bronchodilation. In bronchofibroscopy, we identified a subglottic mass, associated with stenosis and reduction of the airway caliber, without response to mechanical dilatation. The anatomic-pathological study revealed: "intense infiltrate rich in plasmocytes and polymorphonuclears, vascular structures ectasias with presence of swollen endothelia and associated inflammatory signs ". We also found several pulmonary nodules on thoracic CT. The patient fulfilled cyclophosphamide cycle, associated with high dose corticosteroid therapy, with a satisfactory response within a few days and disappearance of subglottic mass and pulmonary nodules after 3 months of immunosuppressive therapy.

Conclusion

This case shows a rare evolution of GPA relapses, with fast symptomatic resolution and complete remission in 3 months. Some studies have shown that complete remission of GPA with glucocorticoid and cyclophosphamide was achieved at a median of 3 months of treatment, however, the treatment of GPA relapses continues to be discussed, especially the role of rituximab, increasingly used in cases of failure of initial therapy.

AUTO1-0511
VASCULITIDES, HORMONES AND AUTOIMMUNITY

IMMUNOLOGICAL AND HISTOPATHOLOGICAL FEATURES OF VASCULITIS IN AN OBSERVATIONAL STUDY IN A MEDICAL COLLEGE HOSPITAL

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Background

Vasculitis, the condition that involves inflammation in the blood vessels due to immune system attacking blood vessels. Chapel Hill Consensus Conference categorizes noninfectious vasculitis based on the type of vessels involved: large vessel, medium vessel & small vessel vasculitis. In this study we see the prevalence of types of vasculitis in a tertiary hospital and their clinical manifestations.

Method

Patients with vasculitis were reviewed retrospectively for 6 months from specialties: Rheumatology, Nephrology, Dermatology and their clinical profile, immunology, imaging and histopathology were analyzed, after obtaining consent from patients.

Results 30 patients reviewed (M:F 13:17). Mean age, 33 years (12-73). Of these, Cutaneous vasculitis formed the major group (17) followed by Takayasu (8), ANCA (5).

Erythematous rash was the common presentation in ANCA and Cutaneous vasculitis while, abdominal pain, limb claudication were common in Takayasu vasculitis. Inflammatory markers were raised in most patients.

Figure:-1

Diagnosis	No of Patients
SLE, RA, Cutaneous vasculitis (overlap syndrome)	1
Wegner granulomatosis (C-ANCA)	3
Churg Strauss Syndrome (P-ANCA)	2
Henoch-Schonlein purpura	3
C1q Nephropathy	1
Sjogren's	1

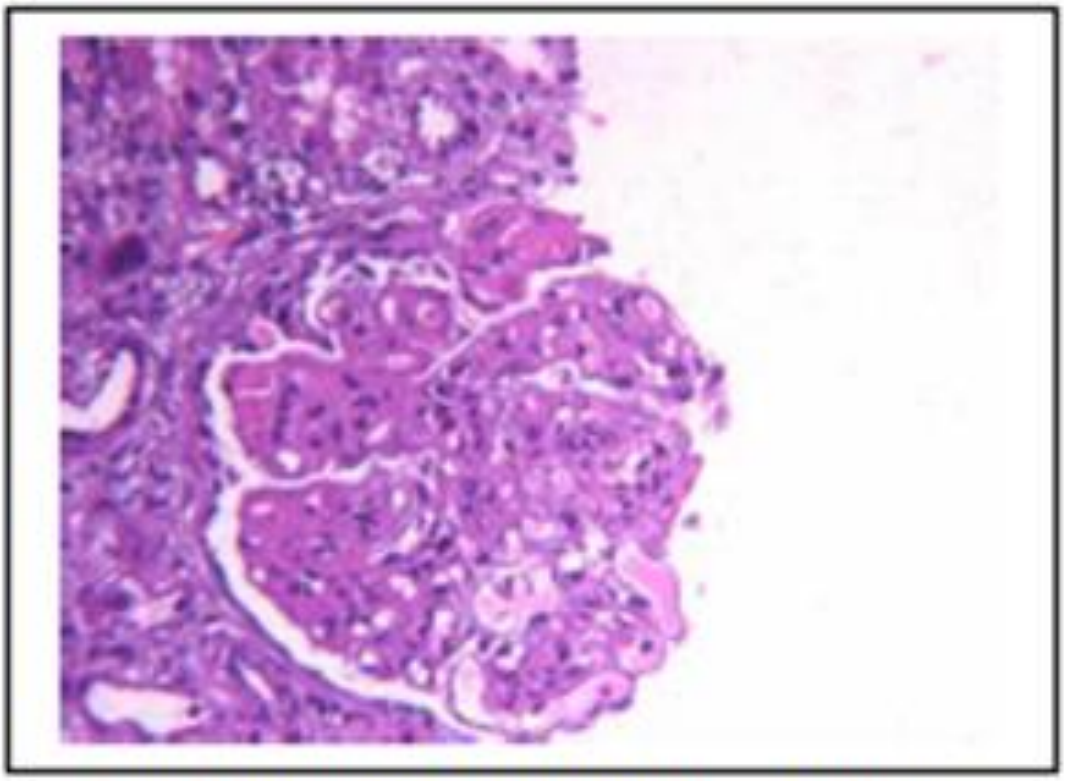
Patients with Takayasu had MR Angiogram showing Subclavian artery renal artery / abdominal aorta narrowing.

Histo-pathologically:

1. Patients with leucocytoclastic vasculitis exhibited neutrophilic infiltration, endothelial swelling.

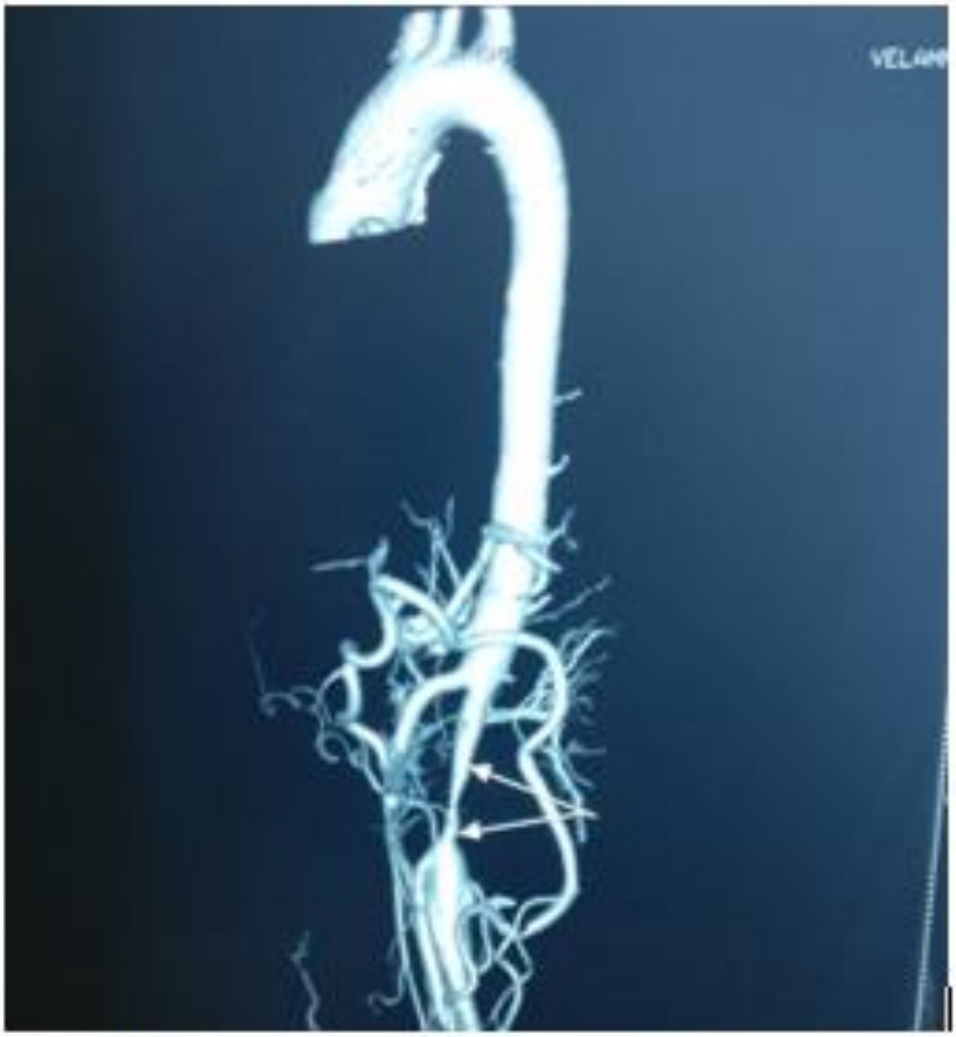
2. Few patients with ANCA vasculitis had nephritis with biopsy showing focal necrotizing vascular lesion with vascular infiltrates.

Figure: 2



Renal biopsy showing focal necrotizing vascular lesion with vascular infiltrates.

Figure: 3



MR Angiogram showing abdominal aorta stenosis

All had Corticosteroids for acute remission. Systemic vasculitis patients had Cyclophosphamide (NIH Protocol) with Azothioprine / Methotrexate / Mycophenolate. Review showed one of the patients with Takayasu vasculitis had re-stenosis of by-passed vessel, while others are in remission with immunomodulation.

Conclusion

1.Incidence of vasculitis is increasing
2.Immunological and Histopathological studies help in definitive diagnosis and prognosis.

AUTO1-0686
VASCULITIDES, HORMONES AND AUTOIMMUNITY

ANCA-ASSOCIATED PAUCI-IMMUNE GLOMERULONEPHRITIS: ¿ALWAYS PAUCI-IMMUNE?

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Background

ANCA-associated glomerulonephritis (GN) is considered a “pauci-immune” disease. However, it is not unusual for renal biopsies to exhibit some immune deposition (ID) within glomeruli on immunofluorescence (IF).The aim of this study was to evaluate the prevalence and clinical significance of immune deposits in ANCA GN.

Method

We included retrospectively all patients with biopsy-proven ANCA GN between January 2002 and May 2013. Patients were divided into 2 groups: Group A: biopsy without IC deposits (less than 2+ intensity of immunostaining) and Group B: biopsy with IC deposits (more than 2+ intensity of immunostaining). IF included Ig (IgG, IgA and IgM) and complement components (C3 and C1q).

Results

Fifty-three patients (75.4% females) were included. Typical pauci-immune GN was found in 39 patients (73.5%, group A). In 14 patients (26.4%, group B) histopathological examination revealed substantial deposition of Ig or complement in the mesangium and/or along the glomerular capillary wall. C3 deposition on the capillary wall was the most frequent finding (64.2%). Patients in group B demonstrated significantly more 24 h proteinuria (mean 0.8 (SD: 7.6) vs 1.6 (SD: 10.7), p= 0.0036). No differences between groups were found related to age, gender, renal function or response to treatment.

Conclusion

In ANCA GN a substantial percentage of patients have evidence of Ig or C3 deposition in renal biopsies (26.4%). In this subgroup, ID was associated with a significantly greater degree of proteinuria. Further clinical and basic research is needed to elucidate the significance of ID deposition in ANCA GN

AUTO1-0160
VASCULITIDES, HORMONES AND AUTOIMMUNITY

CARDIOVASCULAR INVOLVEMENT IN SYSTEMIC RHEUMATIC DISEASES: AN INTEGRATED VIEW FOR THE TREATING PHYSICIANS

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Background

Systemic autoimmune diseases can affect various kinds of organs including the kidney, the skin, soft tissue and the bone. Among others, cardiovascular involvement in rheumatic diseases has been shown to affect myocardium, pericardium, cardiac vessels, conduction system and valves, eventually leading to mortality. However, the cardiovascular involvement in rheumatic disorders has not been focused so much.

Method

In this review, we highlighted acute and chronic cardiovascular complications involving the pericardium, myocardium, valves, (premature) atherosclerosis, ischemia and conduction abnormality in various autoimmune diseases. We thoroughly discuss the prevalence and the characteristics of cardiovascular involvement in rheumatic diseases and describe the potential cardiotoxicity of anti-rheumatic drugs.

Results

Systemic rheumatic disease can be associated with cardiac complications, either attributable to the disease per se or damage accrual due to insufficient management. Different disease has a distinct pattern of cardiac involvement, but the main affected regions are myocardium, pericardium, valves, coronary vessels and the conduction system. Thus far, despite deciphering the pathogenesis of the respective disease, management has largely focused on the control of the respective disease and the inflammatory process. As a result, the true impact of heart involvement was largely neglected, which in turn is a major contributor to the higher mortality observed in most of the discussed entities.

Conclusion

In conclusion, early management of CVD risk factors seems mandatory in high risk rheumatic patients and further therapeutic approaches may be tailored according to the respect entity and the patient’s symptoms to improve the long-term outcome and prognosis of patients.

AUTO1-0982
VASCULITIDES, HORMONES AND AUTOIMMUNITY

PROLACTIN, MMP-3 AND IL-2R AS AN ALTERNATIVE BIOMARKERS OF INFLAMMATORY STATE IN RA AND PSA PATIENTS

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Background

Rheumatoid (RA) and psoriatic arthritis (PsA) are systemic inflammatory diseases, with disorders of synovial tissue, where we are looking for new biomarkers that would demonstrate a pathological changes, especially in patients with low disease activity.

The aim of the study was to assess the applicability of prolactin (PRL), metalloproteinase-3 (MMP-3) and Interleukin 2 Receptor (IL-2R) as alternative parameters of inflammation.

Method

The study group consisted of 28 PsA patients (42±12 age), 32 RA patients (48±16 age) and 15 healthy subjects (44±11 age). In blood samples were determined: CRP, WBC, ESR, PRL, MMP-3 and IL-2R. Statistical analysis was performed using Statistica 12 PL (StatSoft, USA).

Results

CRP, WBC, ESR were similar in RA and PsA patients, while MMP-3, PRL and IL-2R were higher in RA than PsA patients. There was no correlation between the conventional markers of inflammation and MMP-3, IL-2R and PRL in the control group and patients with PsA. In contrast, patients with RA showed a positive correlation between CRP and PRL (p=0,021), ESR and PRL (p=0,047), ESR and IL-2R (p=0,019), WBC and MMP-3 (p=0,010), WBC and IL-2R (p=0,021).

Conclusion

The serum MMP-3, IL-2R and PRL in RA patients show a positive correlation with classical inflammatory markers, which indicates the possibility of using new biomarkers to assess the disease activity of patients with RA. Especially that MMP-3, as an enzyme released by inflamed joint fibroblasts, enables the detection of patients at high risk of pathological changes in the joints at an early stage of the disease.

AUTO1-1013
VASCULITIDES, HORMONES AND AUTOIMMUNITY

REFRACTORY ESSENTIAL MIXED CRYOGLOBULINEMIA VASCULITIS WITH SEVERE RENAL INVOLVEMENT

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Background

Essential mixed cryoglobulinemic renal vasculitis is classically associated with infections, malignancy and autoimmune diseases, but may be idiopathic. Prognosis in patients with grave manifestations is often poor.

Method

We report a case of a 40 year old woman, two weeks after delivery for preeclamsia who was hospitalized with nephritic syndrome and acute renal failure.

Results

Initial findings included high blood pressure, nephritic range proteinuria, low complement C4 and normal complement C3. A renal biopsy was performed and compatible with renal cryoglobulinemia vasculitis. Further tests revealed cryoglobulinemia and a positive rheumatoid factor. Autoimmune serology, hepatitis tests and HIV were negative. Upon development of a rash, a punch skin biopsy confirmed the diagnosis of vasculitis.

Intensive search for a precipitating factor disease was futile except for light chains on urinalysis and monoclonal peaks on serum immune-electrophoresis.

Therapy was initiated with high dose steroids and IV cyclophosphamide. Without response, plasma exchange and dialysis were added. Treatment with cyclophosphamide was discontinued due to pancytopenia and replaced with rituximab which was later discontinued due to severe peripheral neuropathy. Therapy with bortezomib was initiated after a bone marrow biopsy which demonstrated IgM Kappa plasma cells, with transient clinical improvement followed by disease exacerbation. Thereafter, the only therapy was dialysis and plasma exchange. Despite several intensive lines of therapy, the patient developed a masive intracerebral hemmorrhage and succumbed in the intensive care unit following 8 months of hospitalization.

Conclusion

Mixed cryoglobulinemia with multiple organ involvement and without a clear underlying cause is more resistant to therapy and may be fatal.

AUTO1-1027
SHORT ORAL DISCUSSION 1 - INNOVATION IN AUTOIMMUNITY (STATION 1)

VANADIUM PENTOXIDE DIFFERENTIALLY MODULATES CXCL8 AND CXCL11 CHEMOKINES SECRETION IN DERMAL FIBROBLASTS

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Background

Vanadium is a grey metal wih different states of oxidation, and vanadium pentoxide (V_2O_5) is the most usual form. All vanadium compounds are considered toxic. Vanadium workers have shown increases in skin rashes (as atopic dermatitis). However no *in vivo* or *in vitro* studies have evaluated the effect of exposure to vanadium in dermal fibroblasts.

Method

The aim of this study was to evaluate the effect of V_2O_5 on proliferation, and chemokine (C-X-C motif) ligand (CXCL)8, and CXCL11 secretion in dermal fibroblasts.

Results

Our data show that V_2O_5 stimulates the secretion of CXCL8, and of the interferon (IFN)-γ dependent chemokine CXCL11, in dermal fibroblasts, but has no effect on their proliferation. V_2O_5 synergistically increases the effect of IFN-γ on CXCL11 secretion. Moreover, V_2O_5 synergistically increases the effect of the tumor necrosis factor (TNF)-α on CXCL8 secretion, and abolishes the inhibitory effect of IFN-γ.

Conclusion

On the whole the induction of CXCL8, and CXCL11 chemokines secretion by V_2O_5 could lead to the appearance and perpetuation of an inflammatory reaction into the dermal tissue. Future investigations are necessary to evaluate dermal integrity, and manifestations in subjects occupationally exposed, or living in polluted areas.

AUTO1-1026
SHORT ORAL DISCUSSION 1 - INNOVATION IN AUTOIMMUNITY (STATION 1)

CXCL9 AND CXCL10 CHEMOKINES SECRETION BY VANADIUM PENTOXIDE IN THYROID CELLS

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Background

The metal vanadium exists in different states of oxidation (-1, 0, +2, +3, +4, and +5), and its most common form in commercial products is vanadium pentoxide (V_2O_5).
A carcinogenic role of vanadium has been recently proposed on the thyroid gland, even if no *in vivo* or *in vitro* studies have evaluated thyroid disruption in humans and/or animals after exposure to vanadium.

Method

In this study we evaluate the effect of V_2O_5 on proliferation, and (C-X-C motif) ligand (CXCL)9, and CXCL10 chemokines secretion in normal thyrocytes.

Results

V_2O_5 has no effect on thyrocytes viability or proliferation, but it induces the secretion of T-helper (Th)1 chemokines into the thyroid, synergistically increasing the effect of Th1 important cytokines, as interferon (IFN)-γ and tumor necrosis factor (TNF)-α.

Conclusion

Our data show that V_2O_5 induces the secretion of Th1 chemokines into the thyroid, synergistically increasing the effect of Th1 important cytokines such as IFN-γ and TNF-α, leading to the induction and perpetuation of an inflammatory reaction into the gland. Future evaluations will be necessary to investigate thyroid function, and nodules, in occupationally exposed subjects, or living in polluted areas.

AUTO1-0876
SHORT ORAL DISCUSSION 1 - INNOVATION IN AUTOIMMUNITY (STATION 1)

EVALUATION OF TISSUE SPECIFIC AUTOANTIBODIES IN FIBROMYALGIA PATIENTS WITH SICCA AND/OR XEROSTOMIA

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Background

Fibromyalgia patients sometime complain of sicca symptoms, vice versa, Sjögren's syndrome (SS) patients also complain of fibromyalgia symptoms. There is literature questions the interplay of these two disorders. Novel tissue specific autoantibodies (TSA): SP-1, CA6, and PSP, were described in early stage of SS. TSA present themselves before the classic autoantibodies: SSA/Ro, SSB/La, ANA, and RF. This study will examine the relationship between SS and fibromyalgia by testing fibromyalgia patient also complain of sicca symptoms, for Sjögren's related biomarkers.

Method

Cohort of patients presented with symptoms of fibromyalgia, meeting preliminary criteria, were further questioned about sicca symptoms. Patients with sicca symptoms but did not meet criteria for SS were selected for this study. Serum was sent to Immco Diagnostics for testing of Sjögren's related biomarkers

Results

271 patients were selected for this study. 29.8% (81) tested positive for SS, among them, 22.8% (71) were positive for TSA, 9.4% (29) were positive for the classic Sjö markers, and 2.3% (7) were positive for both. Further analysis of patient positive for the TSA (n=71), 74.5% (53) were positive for SP-1, 8.5% (6) were positive for CA6 and 44.7% (32) were positive for PSP. 68.1% (48) of these patients were positive for only one of the TSA and 23 (31.9%) were positive for more than one TSA.

Conclusion

About 1/3 of fibromyalgia patients tested positive for SS related biomarkers, with majority being positive for TSA. This suggests that autoimmunity, specifically early stage of Sjögren's syndrome, may be a confounding variable in the pathophysiology of fibromyalgia.

AUTO1-0956
SHORT ORAL DISCUSSION 1 - INNOVATION IN AUTOIMMUNITY (STATION 1)

DEPRESSION ISSUE IN PATIENT WITH JIA

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Background

Depressive syndrome is commonly found in children suffering from chronic diseases, which is also present in patients with JIA. This study proposed to analyze depression's incidence in children with JIA. We also monitored the evolution of depression with the improvement of the disease under treatment.

Method

We followed 45 patients suffering from JIA, according to ILAR. The assessment of depression was made using the Hamilton scale adapted for children by us. This scale consists of 11 fields with multiple questions, the evaluation being made by counting the score. The scale assesses overall depression intensity. It has a maximum score of 28 points, and one with 8 points defines the depression.

Results

The results obtained using the Hamilton scale showed that from the total of 45 patients suffering from JIA, 11(24%) experienced mild depression, 3 (7%) moderate depression and 8 were borderline. 23 children didn't experience the depressive syndrome. In the control group depression was found in only 5% of subjects. The most appropriate treatment has been applied, and after this symptoms of depression have been improved and the depression score has decreased.

Conclusion

The Hamilton questionnaire adapted for children is easy to apply and it is an important tool for assessing depression.

Depression has been present in one third of investigated patients with JIA.

The symptoms of depression have been correlated with disease activity.

The Hamilton questionnaire adapted for children was first applied in Romania in this study.

Depression does not influence the disease, but the disease induces depression.

AUTO1-1022
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

IVIG IN PEDIATRIC APL RELATED MOTOR NEUROPATHY

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Background

We report a paediatric clinical case characterized by a motor neuropathy in presence of persistent LAC positivity resembling a non-thrombotic neurological clinical manifestation related to antiphospholipid antibodies (aPL).
A healthy, nine-year-old girl abruptly presented with gait disturbance, frequent falls, progressive increasing difficulty climbing stairs, jumping and rising from the ground. When she was admitted to our Pediatric Neurology Unit neurological examination showed mild muscular weakness and tendon reflexes absent at the lower limbs, incomplete Gowers sign, difficulty walking on heels, jumping and instable static and dynamic balance.

Method

She performed neuroimagin, electrophysiological and laboratory assessments.

Results

Brain and medulla magnetic resonance imaging were negative whereas electroneurography at the lower limbs showed findings compatible with motor neuropathy. Infective, immunologic and autoimmunity assessments were all negative except for LAC positivity. Because of the immune hypothesis intravenous immunoglobulin treatment (IVGI) was started at the dose of 0.4 g/kg/day for 5 days. The treatment was well tolerated and an immediate improvement of the pattern of ambulation and the balance were noted. In the following months, a further improvement until a complete resolution was obtained after the second and third IVIG dosing (see movie). Persistent Lac positivity was found to be present three months later.

Conclusion

Our findings suggest the importance of the early treatment of immunomodulant therapy in order to have a successfully outcome. It is also important to check aPL in children with a rapid onset of neurological signs in order to provide beneficial use of IVGI in the treatment of pediatric aPL neurological conditions.

AUTO1-1030
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

SUBFOVEAL CHOROIDAL THICKNESS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect the vascular system in several organ systems. Likewise, retinal and choroidal vasculature commitment has been described, particularly in patients with poor systemic control. Subclinical choroidal changes have been described in several systemic diseases with vascular involvement.

This study aims to study subfoveal choroidal thickness in SLE patients without ophthalmic manifestations.

Method

51 patients with SLE and 26 healthy controls were enrolled in the study. Among the patients with SLE, 14 had the diagnosis of neuropsychiatric SLE (NPSLE). A complete ophthalmological evaluation was performed in all patients, including optical biometry to measure axial length. Subfoveal choroidal thickness was measured with spectral domain optical coherence tomography using enhanced depth imaging software.

Results

Mean subfoveal choroidal thickness in SLE patients was 280.78(84.60)µm and 254.31(64.61)µm in healthy controls. The difference was not statistically significant (p=0.11). 19 patients had active disease (SLEDAI > 3). Patients with active disease presented thicker choroids (297.11(88.81)µm vs 270.45(79.14)µm; p=0.29) when compared to non-active-SLE, but the difference was not significant. There were no significant differences in subfoveal choroidal thickness between NPSLE and non-NPSLE. Disease duration or hydroxychloroquine treatment time also had no impact in subfoveal choroidal thickness.

Conclusion

SLE patients tend to have higher subfoveal choroidal thickness than healthy controls. Choroidal thickness also tends to be higher in patients with active disease, however this parameter does not seem to be a sensitive marker of systemic disease activity in patients without ophthalmic manifestations.

AUTO1-0770
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

DFS70 CONFIRMATION IS NOT ENOUGH! TO MANAGE AN ANTI-DFS70-LIKE PATTERN IN THE REAL-LIFE.

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Background

Anti-DFS70 antibody identification and subsequent confirmation is clinically important because the presence of anti-DFS70 as the unique antibody responsible for anti-nuclear antibody (ANA) positive results, may help exclude an underlying systemic autoimmune disease, significantly changing the follow-up of a patient. In addition, a high titre DFS70 pattern may mask other ANA patterns. For this reason, a large ANA screening test should be performed to ensure not to lose any other clinically relevant antibody.

Method

When a DFS70-like ANA pattern is found on HEp2 cells during the standard indirect immunofluorescence (IIF) session, we apply a reflex algorithm that associates anti-DFS70 confirmation with a large CTD screen test performed by chemiluminescence (CLIA) (Inova Diagnostics).

Results

Case report: Anti-DFS70 antibodies were strongly suspected when assessing ANA by IIF in a 54 year-old female patient diagnosed with pulmonary sarcoidosis. Confirmatory anti-DFS70 and CTD-screen by CLIA provided high positive results for both tests (253 CU/ml and 98 CU/ml, respectively; cut-off 20). Using a lineblot assay we identified anti-PCNA antibodies at high titre. These findings were replicated after 30 days. In this case, the typical PCNA-associated pleomorphic pattern was completely masked by the anti-DFS70 pattern and only the combined use of the CTD-screen and of the lineblot tests enabled recognition of the antibody.

Conclusion

Therefore, it is of the outmost importance not only to confirm anti-DFS70 antibodies, but also to ensure that it is the only specificity associated to ANA positivity. Association of a large CTD screening test looks very useful for a rapid and accurate report to clinicians.

AUTO1-0721
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

DEPRESSION IN LUPUS AND RHEUMATOID ARTHRITIS – A COMPARATIVE STUDY SEARCHING FOR LUPUS-SPECIFIC CONTRIBUTORS TO DEPRESSION.

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Background

Depression and anxiety cause severe loss of quality of life for patients with Lupus. The factors contributing to these psychological manifestations in lupus are difficult to disentangle. This study compared clinical, psychological and socio demographic characteristics in lupus patients, depressed patients, and Rheumatoid Arthritis patients to discover

Method

Physiological, clinical, and psychosocial data were collected from 77 patients. ELISA was used to measure cytokine levels. Univariate and Multivariate analyses were used to compare the patient populations and identify correlations between key physical, laboratory and psychological indicators.

Results

Pain, IL-6, and Pittsburg quality sleeping index values were all significantly higher in SLE patients compared to the healthy control group ($p < 0.001$, $p = 0.038$, and $p = 0.005$, respectively). Anxiety levels were significantly higher in SLE patients compared to healthy and RA control patients ($p = 0.020$ and 0.011, respectively). Serum IL-10 concentrations, relationship assessment scale, and fatigue severity scale values were found to be correlated with depression among the SLE patients ($p = 0.036$, $p = 0.007$, and $p = 0.001$, respectively). Relationship assessment and fatigue severity scale scores were found to be the best indicators of depression in the SLE patients group ($p = 0.042$ and 0.028, respectively).

Conclusion

Fatigue Severity, relationship satisfaction, and IL-10 concentrations are indicators of depression in lupus patients. Despite also suffering from the pain and disability that accompanies chronic autoimmune disease, the Rheumatoid Arthritis patients had less anxiety and better relationship scores.

AUTO1-0882
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

INFLAMMATION, AUTOIMMUNITY, PSYCHOSIS AND COGNITION IN 22Q11.2 DELETION SYNDROME

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Background

22q11.2 deletion syndrome (22q11.2DS) is a neurogenetic disorder whose phenotype includes high rates of a schizophrenia-like psychotic disorder and immune system abnormalities. Thus, 22q11.2DS is an ideal model for studying the relationship between psychosis and inflammation.

Method

Forty-nine individuals with 22q11.2DS (13 with psychotic disorders and 36 without psychotic disorders) and 30 age- and sex-matched healthy controls underwent psychiatric and cognitive assessments. Blood samples from all participants were drawn and analyzed for several inflammatory and autoimmune markers: CRP, cytokines (IL6, IL-10, TNFα, IL-1ra) and autoantibodies (e.g. anti-dsDNA, ANA, Anti-ribosomal P).

Results

The 22q11.2DS participants had elevated levels of IL-6, TNFα and IL-10 compared to controls. Furthermore, the psychotic 22q11.2DS participants had higher levels of IL-6 and IL-6/IL-10 ratio (used as an indicator for pro-inflammatory activation) compared to the nonpsychotic 22q11.2DS individuals and controls. IL-6 levels and the IL-6/IL-10 ratio correlated with the severity of the cognitive deficits in the 22q11.2DS participants. There were no significant differences between cohort sub-groups in CRP or autoantibodies levels.

Conclusion

Our preliminary findings indicate an involvement of inflammatory or autoimmune processes in the pathophysiology of psychosis and cognitive deficits in 22q11.2DS and are in line with the accumulating evidence for the role of neuroinflammation in nonsyndromic schizophrenia.

AUTO1-0630
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

ANTIBODIES IN PATIENTS WITH CHRONIC TENSION TYPE HEADACHE AND CHRONIC MIGRAINE: IS THERE A LINK BETWEEN HEADACHE AND AUTOIMMUNITY?

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Background

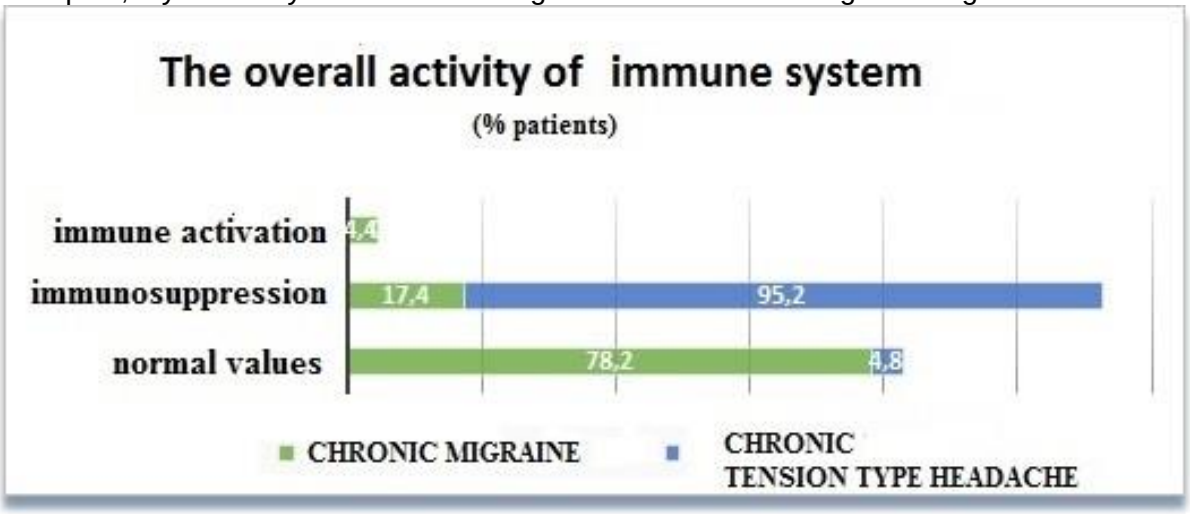
Neuroimmunological impairments are not only an important part of headache pathogenesis, but also can be a risk factor for the headache chronization, its atypical course and formation of resistance to pharmacotherapy.

Method

The survey of 44 patients with chronic tension-type headache (CTTH) (n=21) and chronic migraine (CM) (n=23) was conducted by: physical and neurological examination, psychological evaluation of stress level and stress resistance, immune assay "ELI-Test" (Medical Research Center "Immunculus") to determine serum levels of 33 IgG autoantibodies (a-Abs) against antigens of major organs and systems of the human body.

Results

The majority of CTTH patients has laboratory immunosuppression 95,2% , in contrast to CM group 17,4% ($p<0,01$). These data correlate with higher stress level by RSM-25 ($p<0,01$) and lower stress resistance level ($p<0.05$) in patients with CTTH. In patients with CM we found significantly more abnormalities in a-Abs level against NF-200, Voltage-dependent Ca channels, ds-DNA, β2-glycoprotein-1, peripheral insulin receptors, Tg, TSH receptor and membrane antigen of adrenal medulla cells. Patients with CTTH presented a significantly more deviation of a-Abs level against μ-opioid receptors, β-endorphin, myocardiocyte membrane antigen and membrane antigen of large intestine.



Conclusion

The laboratory data confirm significant contribution of psychoneuroendocrine-immune interactions disturbance, peripheral and central sensitization in the pathogenesis of CM; disturbance of balance in autonomic nervous system, "bodily distress syndrome", pronounced muscular spasm and insufficiency of descending inhibitory influences in the pathogenesis of CTTH. Based on results of the experiment we can suggest the significant role of stress in the headache pathogenesis and development of neuroimmunological imbalance.

AUTO1-0884
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

PERFORMANCE ANALYSIS OF BAM AND BPN FOR CHARACTER RECOGNITION

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Background

The Overall research work contains a number of procedural steps. Such as converting a black and white image to grayscale and various image processing steps, learning a pattern using Back-propagation Neural Network (BPN) and Bidirectional

Method

The paper describes the recognition of character using BAM (Bidirectional Associative Memories) and multiple feed forward Back Propagation Network (BPN) algorithm. To do this, characters are scanned first with a scanner or written in any paint program and save the cha

Results

In the above diagram the performance of BAM and BPN have been compared. From the above diagram it is clear that BPN shows better performance than BAM. The performance can also be increased by choosing proper parameter of backpropagation network (learning rate, momentum term etc).

Conclusion

The field of character recognition has been an active topic of research and development for many years. The character recognition system is used to identify different types of character. Pattern recognition system has two principle tasks: feature extraction and classification. This experimental network can be recognized more than one character at a time even though a minimal distorted pattern is gives as an input. However this recognition system could be used to implement for various identifying purposes. The proposed recognition system

AUTO1-0971
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

A CASE REPORT OF TAKAYASU ARTERITIS WITH SEVERE RETINOPATHY

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Background

Background: Takayasu arteritis (TA) is a chronic, relapsing, progressive panarteritis with preferential large-vessels involvement. Fewer TA adolescent patients present with the first symptom of severe ocular lesion. Here, we report a case of a female adolescent afflicted with TA and presenting with severe retinopathy.

Case presentation: A 13-year-old female presented with a progressively severe ocular pain and loss of vision of the right eye. She also complained of recurrent of syncope and numbness of her left side. The CTA of carotid arteries pointed out severe stenosis at the origins of the brachiocephalic-vessel, bilateral carotid arteries and bilateral subclavian arteries with partial occlusion. The ophthalmic testing indicated largely decreased vision in the right eye with mydriasis and disappearance of light reaction. The fundus examination showed the boundary of right optic disk was blurring. The retinal vessels were segmental filling with arteries dilated and the veins narrow. The right retina was edematous in off white with scattered cotton-wool spots. The follow-up ophthalmic testing revealed improvement after appropriate therapy by tocilizumab and methylprednisolone, and followed by prednison and ciclosporin.

Method

N/A.

Results

N/A.

Conclusion

Severe ocular lesion as the first symptom in TA adolescent patients is rare but severe, which can be improve by appropriate therapy.

AUTO1-0324
SHORT ORAL DISCUSSION 10 - CENTRAL NERVOUS SYSTEM AND AUTOIMMUNITY: EYE, SMELL AND PSYCHIATRY (STATION 2)

STROKE AMONG RA PATIENTS: DOES AGE MATTER? A REAL-LIFE STUDY

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Background

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disease that affects the joints and known to be associated with cardiovascular morbidity. However, the association between RA and stroke among different age groups has not been explored. The objective of our study was to evaluate the association between RA and stroke in different age strata.

Method

Cross-sectional study, utilizing the database of Israel's largest healthcare provider.

Proportion of stroke was compared between patients diagnosed with RA and age- and gender-matched controls. Study sample was divided into two age groups: young (≤ 65 years) and elderly (> 65 years). Multivariable analysis was performed using logistic regression.

Results

The study included 11,782 RA patients and 57,973 age- and sex-matched controls. RA patients, primarily young, had more cardiovascular risk factors than controls. Stroke rates were significantly elevated among young RA patients in comparison with controls (3.74% vs. 2.20% respectively, $P < 0.001$). In multivariate analysis, RA was found to be independently associated with stroke (OR 1.18, 95% CI 1.09, 1.28).

Conclusion

RA is independently associated with stroke, especially amongst RA patients under 65 years, for whom cardiovascular risk factors were more prominent. Physicians should advise RA patients to manage their risk factors strictly.

AUTO1-0685
SHORT ORAL DISCUSSION 11 - STANDARDIZATION OF DIAGNOSTICS (STATION 1)

RELIABILITY OF SIMPLE CAPILLAROSCOPIC DEFINITIONS TO DESCRIBE CAPILLARY MORPHOLOGY IN RHEUMATIC DISEASES

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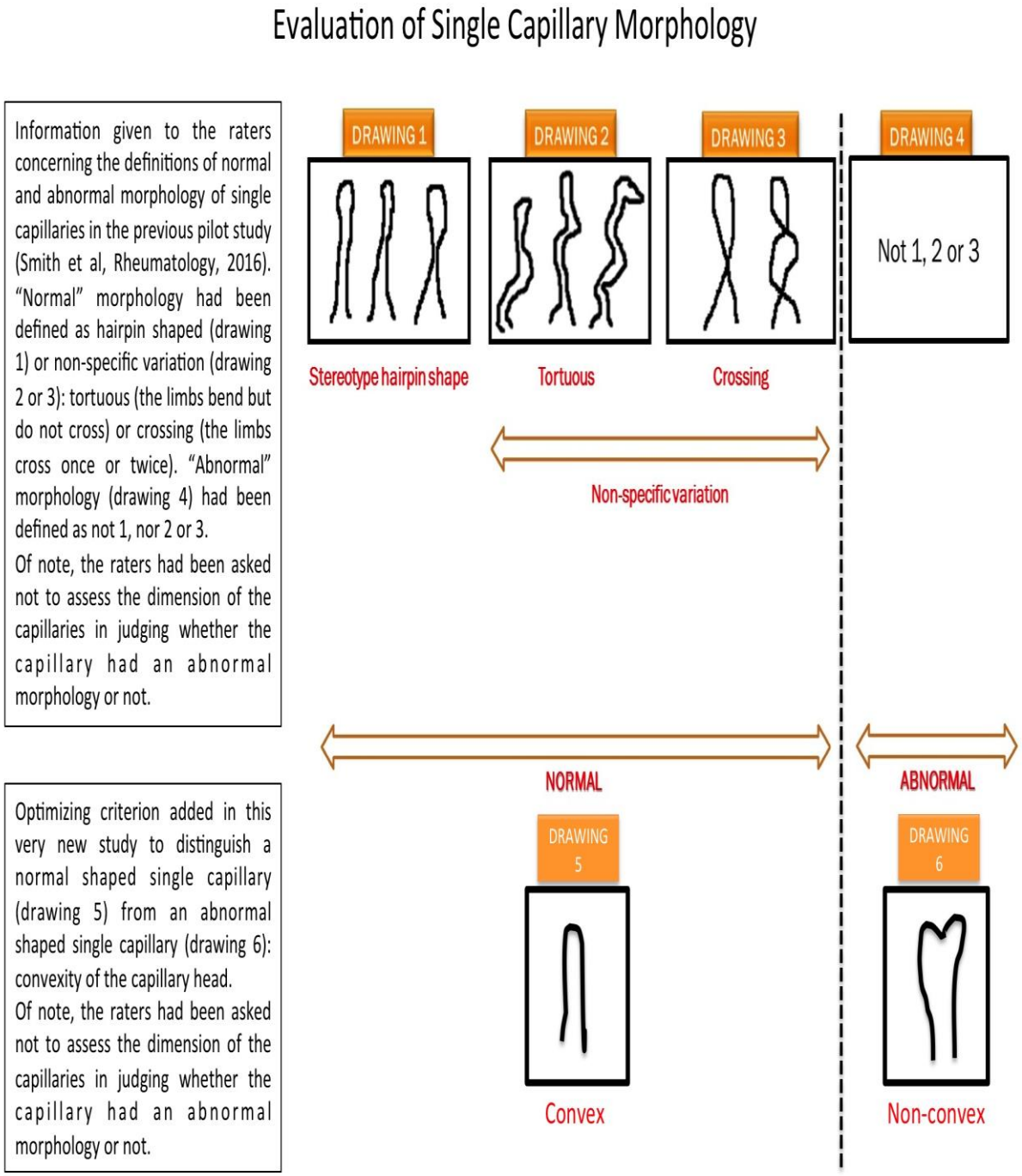
Background

The EULAR study group on microcirculation in rheumatic diseases has previously proposed simple definitions for interpretation of capillaroscopic morphology of single capillaries, which resulted in moderate reliability. The aim of this study is to further optimize these definitions.

Method

To fine-tune the existing definitions (normal—hairpin, tortuous or crossing; abnormal—not hairpin, not tortuous and not crossing), convexity of the capillary head was added as a condition to be evaluated as normal (figure). Thirty images with good visibility of single capillaries were presented to the attendees of the seventh EULAR Course on capillaroscopy (Genoa 2016). Attendees (n = 119) were asked to categorize themselves into one of the following levels of expertise in capillaroscopy: no experience (novices); less than 5 years of experience and more than 5 years of experience. Also, 5 independent experts (AH, FI, AS, MC and VS) evaluated the capillaries. Inter-rater agreement was assessed by calculation of the Cohen's kappa between each rater pair of all possible combinations of attendees and the gold standard (GS) and then averaged to provide the Light kappa. In addition, the Cohen's kappa scores between each attendee and the GS were averaged to obtain a mean index of reliability of the attendees to the GS.



Results

The resulting Light kappa based on 30 capillaries for all EULAR course attendees (experienced, moderate experienced and novices) and the 5 independent experts are depicted in table 1, together with the mean Cohen's kappa (compared to the GS).

Group of raters	Mean kappa (95% CI)	Light's kappa
All attendees (n=119)	0.81 (95% CI: 0.79-0.83)	0.78
Novices (n=69)	0.80 (95% CI: 0.77-0.83)	0.77
Moderate experienced (n=41)	0.81 (95% CI: 0.77-0.85)	0.78
Experienced (n=9)	0.83 (95% CI: 0.78-0.88)	0.84
Independent experts (n=5)	0.81 (95% CI: 0.71-0.92)	0.82

Table 1: Mean Cohen's kappa (95% confidence interval, CI) for the different groups of raters versus the golden standard and Light's kappa for the different groups.

Expertise in capillaroscopy of the attendees of the EULAR course in capillaroscopy was divided into the following groups: no experience (novices); less than 5 years of experience (moderate experienced) and more than 5 years of experience (experienced). N = number of raters.

Conclusion

This study showed excellent reliability of optimized definitions for describing capillary morphology.

AUTO1-0237
SHORT ORAL DISCUSSION 11 - STANDARDIZATION OF DIAGNOSTICS (STATION 1)

DEVELOPMENT OF A SERUM CERTIFIED REFERENCE MATERIAL AGAINST ANTI-LIPOPROTEIN H (ANTI- β2GPI) IgG ANTIBODIES

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Background

Antibodies against Apolipoprotein H (ApoH, formerly known as β2 Glycoprotein I) are the most specific biomarker for the antiphospholipid syndrome. However, large discrepancies between results from different methods are limiting its clinical utility. The availability of a suitable certified reference material (CRM) would provide an anchor point for the standardisation of results and their comparability throughout time. The Joint Research Centre of the European Commission collaborates with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) on achieving this goal.

Method

The development of such a CRM involves various steps, from finding the appropriate starting serum material to feasibility studies, homogeneity and stability testing, as well as characterisation of the mass concentration of the antibody of interest.

Results

Commutability tests so as to confirm the suitability of the starting material are being performed. Upon confirmation, value assignment measurements will be performed by IVD manufacturers using routine anti-ApoH methods and an affinity-purified IgG anti-ApoH calibrant, whose concentration has already been, in turn, determined by nephelometry and turbidimetry. The derived mass concentration of the calibrant is traceable to SI and so will the value for the CRM.

Conclusion

It is expected that with the use of this CRM for calibration and/or quality control of anti-ApoH IgG measurements, together with the appropriate use of internationally combined guidelines and recommendations will significantly reduce inter-laboratory and inter-method variations.

AUTO1-0783
SHORT ORAL DISCUSSION 11 - STANDARDIZATION OF DIAGNOSTICS (STATION 1)

ICAP CONSENSUS: THE PORTUGUESE FROM PORTUGAL MULTICENTRE TRANSLATION CONSENSUS

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Background

The International Consensus on ANA Patterns (ICAP) initiative started in the 12th International Workshop on Autoantibodies and Autoimmunity (IWAA) in 2014, in S. Paulo, Brazil and aimed to achieve consensus on the nomenclature and description of the different morphological ANA patterns observed in the indirect immunofluorescence assay (IIFA) on HEp-2 cells. As a result, three major staining categories were classified:

nuclear, cytoplasmic and mitotic patterns.

This initiative also exposed their work in a internet site www.anapatterns.org that has translations in English, French, Deutsch, Spanish, Chinese and Portuguese either from Brazil and from Portugal.

Method

The authors are Medical Doctors and Pharmaceutical Scientists working in Laboratory Medicine in 5 different sites in Portugal, either public or private, with extensive experience in IIFA and ANA patterns reporting, decided to get together and extend the ICAP work in order to establish a Portuguese national consensus.

Results

Extend the ICAP work in order to establish a Portuguese national consensus.

Conclusion

They recognized that standardization and harmonization in autoimmune diagnostics is of utmost importance but the use and uptake of ICAP ANA patterns site in Portugal will only be possible if the Portuguese translation will be accepted by a large number of Laboratory Professionals.

AUTO1-0074
SHORT ORAL DISCUSSION 11 - STANDARDIZATION OF DIAGNOSTICS (STATION 1)

THE INTER-OBSERVER READING VARIABILITY IN ANTI-NUCLEAR ANTIBODIES (ANA) INDIRECT IMMUNOFLUORESCENCE TEST: A MULTICENTER EVALUATION

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[2]S. Giovanni di Dio Hospital, Immunology and Allergy laboratory, Florence, Italy
[3]Università Campus Biomedico, Unit of Computer Systems and Bioinformatics, Rome, Italy
[4]AST Spedali Civili, Rheumatology Unit, Brescia, Italy
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Background

Recently there has been an increase demand of CAD tools to support clinicians in the field of IIF. Digital imaging can help us to overcome the reader subjectivity.

Method

We evaluated 556 consecutive samples in three laboratories (named A, B, C) expert in IIF field to assess inter-observer variability using digital images reading approach instead of manual visual approach. We acquired 1679 images using HEp-2 cell (MBL) at 1:80 screening dilution according to the conventional procedure. Each expert took 3 different images per sample with an acquisition unit. Digital images have been reclassified from two blinded experts into: positive, negative, weak positive. Positive and weak positive ANA-IIF results were categorized by the predominant fluorescence pattern among six main classes.

Results

We observed a substantial agreement (k 0.602) between centers. The agreement on positive and negative samples is for both larger than 80%.We found low specific agreement values on the weak positive samples. We computed an average overall agreement equal to 74.1%. Satisfactory specific agreement was found for the homogeneous type (77.9%), whereas a poor agreement for nuclear dots(6.9%), combined pattern(22%), and for “other” patterns(13.6%).
Using the gold standard the agreement between each center and the gold standard is larger than agreement between experts both for positive/negative (k 0.777 vs 0.602) and for staining pattern.

Conclusion

Laboratories’ agreement improves using digital images and comparing each single human evaluation to a potential reference data. Solid gold standard is essential for use CAD systems in routine work lab.

AUTO1-0048
SHORT ORAL DISCUSSION 12 - PREGNANCY, SEX HORMONES AND AUTOIMMUNITY (STATION 2)

PROLACTIN, BREASTFEEDING AND AUTOIMMUNE DISEASES.

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Background

Breast milk is not only a completely adapted nutrition source for the newborn but also an impressive array of immune active molecules that afford protection against infections and shape mucosal immune responses. Decisive imprinting events might be modulated during the first months of life with potential health long-term effects, enhancing the importance of breastfeeding as a major influence on the immune system correct development and modifying disease susceptibility. On the other hand, the breastfeeding woman faces a health challenging period in life. During the lactation period, assorted autoimmune patients experience disease relapses, suggesting an active interference from increased plasma levels of prolactin, which can act as a hormone and as a pro-inflammatory cytokine.

Method

Literature review.

Results

Human milk benefits may be explained by the protection against early infections, anti-inflammatory properties, early antigen-specific tolerance induction, and regulation of infant´s microbiome. On the other hand, the role of prolactin in the modulation of the immune system is undeniable, and recent data showed a positive correlation between hyperprolactinemia and systemic lupus erythematosus, rheumatoid arthritis and peri-partum cardiomyopathy patients.

Conclusion

Breastfeeding was associated with a protective role for infant´s against autoimmune phenomena, mainly in type 1 diabetes and celiac disease. However, the benefits of breastfeeding for mothers with autoimmune disorders are debatable.

AUTO1-0615
SHORT ORAL DISCUSSION 12 - PREGNANCY, SEX HORMONES AND AUTOIMMUNITY (STATION 2)

EFFICACY AND SAFETY OF LOW DOSE PREDNISONE FOR THE TREATMENT OF NK-RELATED RECURRENT PREGNANCY LOSS

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Background

Immunological causes of recurrent pregnancy loss (RPL) include NK cell counts over 12%. Prednisone is used during pregnancy in different clinical settings. In vitro studies have demonstrated the immunodulatory role of prednisone on NK cell function. We evaluated the efficacy and safety of low dose prednisone in NK-related RPL.

Method

In a retrospective analysis of clinical data collected prospectively we evaluated the outcome of pregnancy in 30 women who received low dose prednisone and 39 women that were not treated during pregnancy. Prednisone was started at the time of biochemical detection of pregnancy at a dose of 10 mg/day and maintained up to 12 weeks. Primary outcome was the incidence of successful pregnancy. NK cell counts were monitored during pregnancy in the prednisone group.

Results

Baseline (pre-pregnancy) characteristics were similar in both groups including age (36 vs 36 years, p=0.86), number of RPL (2.5 vs 3.1, p=0.20), vitamin D level (23.05 vs 25.07, p=0.77), proportion of primary and secondary RPL (p=0.71). There were 23 women successfully treated in the prednisone group (successful rate 79.31%), and 18 women in the control group (successful rate 46.2%). Size effect in logistic regression was 3.29, 95%CI 1.09-9.84, p=0.034. The incidence of diabetes (p=0.34), hypertension (p=0.44) and infection during pregnancy (p=0.63) was similar in both groups. Gestational age was similar in both groups (36.6 vs 37.1 weeks, p=0.78). A significant decrease in NK-cell level was observed at 6 months in prednisone group.

Conclusion

The potential role of low dose prednisone treatment in prevention of NK-related RPL is suggested.

AUTO1-0598
SHORT ORAL DISCUSSION 12 - PREGNANCY, SEX HORMONES AND AUTOIMMUNITY (STATION 2)

IMMUNOLOGICAL AND INFLAMMATORY “PLAYERS” IN THE HUMAN ENDOMETRIUM

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Background

Endometrium is the inner epithelial lining of the uterus in which the implantation takes place. In the recent years, extended scientific works have shed light on the important role played by the human endometrium during early phases of pregnancy.

Method

review of the literature and of our previous research work

Results

Endometrium is the inner epithelial lining of the uterus in which the implantation takes place. In the recent years, extended scientific works have shed light on the important role played by the human endometrium during early phases of pregnancy. During implantation the ability of blastocyst and trophoblasts to adhere and invade into uterine wall must fit well with an adequate maternal environment in the absence of a well-defined placenta. Among the properties of the endometrium are the inflammatory changes that occur dynamically across the menstrual cycle. Immunocompetent cell composition and inflammatory gene expression pattern in the human endometrium drastically fluctuate from the proliferative phase to the secretory phase.These local immune responses are fine-tuned by the direct or indirect action of the ovarian steroids, estradiol and progesterone, and are essential for successful blastocyst implantation. Meanwhile, studies have been accumulating the evidence that such physiological endometrial inflammatory status is altered in the presence of certain conditions. Given that blastocyst is a semi-allograft for maternal tissue, even subtle alterations in endometrial immunity potentially have a negative impact on implantation process.

Conclusion

In this work we review the role of the immunological players expressed in the human endometrium.

AUTO1-1004
SHORT ORAL DISCUSSION 12 - PREGNANCY, SEX HORMONES AND AUTOIMMUNITY (STATION 2)

NEONATAL LUPUS: EARLY DETECTION WITH A FAVORABLE OUTCOME

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Background

Neonatal Lupus (NL) is a passively acquired autoimmune disease, via transplacental passage of the mother's autoantibodies.

Method

We bring a case of a 34-year-old woman, 21 weeks and 4 days (w+d) pregnant (third gestation, previous 2 were normal) referred to the obstetrics department for a fetal bradycardia of 62 beats per minute (bpm) (normal 110-150bpm). A fetal echocardiography was performed, identifying a complete atrial-ventricular (AV) block, with frequency ratio of 2:1. There were no apparent cardiac malformations or signs of heart failure. The mother denied having any symptoms, namely xeropthalmia/xerostomia, arthralgias, Raynaud's phenomenon, skin or mucosal lesions, eye or heart disease. She tested positive for antinuclear antibodies (titer 1:640) with a fine speckled pattern, and anti-SSA. There were no abnormalities in blood count, renal function nor complement dosage; anti-SSB, anti-dsDNA and the study for antiphospholipid syndrome were negative. She was started on daily dexamethasone 5mg and hydroxychloroquine 400mg.

Results

The fetal heart rate improved to a maximum of 84bpm. A caesarean section was performed at 37w+3d, and the newborn was placed on temporary pacemaker, which was later removed due to heart rate stabilization. There were no visible skin lesions on the newborn. After delivery, the mother stopped all medication, with indication to attend a follow-up appointment.

Conclusion

NL causes almost 95% of congenital AV blocks. It's highly infrequent (2% of gestations), particularly with no underlying autoimmune disease. SSA and SSB autoantibodies are the most frequently associated autoantibodies, specially when in high titer. The maternal disease is asymptomatic in almost half the cases.

AUTO1-0846
SHORT ORAL DISCUSSION 13 - POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS (STATION 1)

COMBINING MYOSITIS SPECIFIC ANTIBODIES SPECIFICITY AND ANTINUCLEAR ANTIBODY PATTERN IMPROVES THE SEROLOGICAL DIAGNOSIS OF IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background:
Myositis-specific antibodies (MSA) are serological markers for the diagnosis of idiopathic inflammatory myopathies (IIM). The diagnostic value of anti-nuclear antibodies (ANA) by indirect immunofluorescence (IIF) on HEp-2 cell in this field is limited because they lack sensitivity (around 50%). MSA profiling by immunoblot (IB) it is increasingly used in the routine work-up. However, IB costs limit its widespread use for screening purposes. We evaluated whether it is possible to identify typical ANA patterns associated to each single specific MSA.
Methods:
Serum samples from 104 patients presenting with myalgia and positive to at least one MSA in the IIM IB profile (MIOS7 and MYOS12 Diver, D-Tek, Belgium) were tested for ANA by IIF on HEp-2000 cells (Immuno Concepts, US). 83 of these patients had a diagnosis of definite IIM, while in 21 cases, the diagnosis was still pending.
Results:
Concordance between the ANA-IIF pattern and MSA was found in 59% (49/83) of patients of the definite IIM group and in 19% (4/21) of patients of the IIM uncertain group ($p<0.001$). In the IIM uncertain group 9 patients out of 21 (44.5%) presented more than one MSA positivity while in the IIM group only 5 out 83 (6%) presented more than one MSA positivity($p<0.001$).

Conclusions:
Considering both MSA result and its corresponding pattern by ANA testing may help to improve the specificity of MSA detection by IB and to confirm the diagnosis of MSA-associated IIM. The monopositivity of the MSA result is an important additional tool to validate the IB result.

AUTO1-0012
SHORT ORAL DISCUSSION 13 - POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS (STATION 1)

ASSOCIATION OF SOLUBLE CTLA4 LEVELS WITH CLINICAL AND HEMATOLOGICAL PARAMETERS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background

Multiple sclerosis (MS) is an autoimmune disease that is characterized by demyelinating lesions affecting the central nervous system and spinal cord which leads to progressive neurological deterioration. Previous studies have associated high serum sCTLA4 with the clinical course of MS and other autoimmune diseases, which contribute the development of the disease

Method

50 MS patients classified according to the 2010 McDonald criteria and control subjects (CS), adjusted by age and sex. Hematic cytometry was measured by automatic hematology analyzer; and serum levels of sCTLA4 were determined by ELISA method. The data was analyzed with STATA v12 software and $p<0.05$ was reported as statistically significant

Results

Levels of hemoglobin ($p=0.004$), ESR ($p=0.001$), lymphocytes ($p=0.013$) and banded neutrophils ($p<0.001$), were more elevated in MS patients than CS group. In addition, levels of sCTLA4 in MS group were higher than CS group (13.44 pg/mL vs 8.94 pg/mL, $p<0.001$). Also, we found an increase of serum levels of sCTLA4 in MS patients with an EDSS of 6-6.5 that MS patients with an EDSS of 0-3.5 (15.45 vs 12.92 pg/dL, $p=0.03$1). Moreover, we found that sCTLA4 is positively correlated with hemoglobin ($p=0.005$) and banded neutrophils ($p<0.001$)

Conclusion

This study revealed that MS patients have high levels of sCTLA4 regarding CS group and these increments correlated with hematological parameters and associated with EDSS. These suggest that sCTLA4 could be used as a new serological marker of diagnostic and progression in MS

AUTO1-1020
SHORT ORAL DISCUSSION 13 - POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS (STATION 1)

COMBINED TESTS FOR RATIONAL REQUEST AND UTILIZATION OF MYOSITIS-SPECIFIC ANTIBODIES AND MYOSITIS-ASSOCIATED ANTIBODIES FOR THE DIAGNOSIS OF IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background

The aim of our study was to evaluate in terms of clinical efficacy the combination of tests for the diagnosis of idiopathic inflammatory myopathies (IIM).

Method

We retrospectively examined 48 patients with an established diagnosis of IIM. ANA were tested by IIF on HEp-2, anti-SSA and anti-Jo1 were detected by CLIA method, MSAs and MAAs by LineBlot method.

Results

46 of 48 (95,8%) patients were positive by at least one of the three methods. 45 of 48 (93,7%) were positive for MSAs and/or MAAs. By CLIA 14/48 (29,2%) were double positive for anti-Jo1 and anti-SSA, 8 (16,6%) were positive for anti-Jo1 and 11 (22,9%) for anti-SSA. The agreement between CLIA and LineBlot for anti-Jo1 and anti-SSA autoantibodies was very good (Cohen's Kappa= 0,831 and Cohen's Kappa= 0,958 respectively). We found a statistically significant correlation between anti-SSA autontibody levels detected by CLIA and anti-Ro52 autoantibody scores by LineBlot (Pearson r=0,71; P=0.0001) and between anti-Jo1 autontibody levels detected by CLIA and anti-Jo1 autoantibody scores by LineBlot (Spearman r=0,88; P<0.0001). Among 26 (54,2%) patients anti-Jo1 negative: 10 (38,4%) were positive for MSAs and/or MAAs, 3 for anti-EJ, 2 for anti-PL12, 3 for anti-MDA5, 2 for anti-SAE and 6 for anti-PM-Scl.

Conclusion

Our findings suggest that when IIM is clinically suspected, a possible diagnostic algorithm includes in a first step the association of the ANA-IIF with a specific test for anti-Ro52 and anti-Jo1, and in a second step, in patients ANA-IIF and CLIA negative or only ANA-IIF and/or anti-SSA/CLIA positive, a myositis profile LineBlot.

AUTO1-0996
SHORT ORAL DISCUSSION 13 - POLYMYOSITIS, MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS (STATION 1)

CLINICAL AND LABORATORY PROFILE OF PATIENTS WITH ANTI-HMGCR ANTIBODIES. CLUES FOR SUSPECTING THIS CLINICAL ENTITY

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Background

Anti-HMGCoAr have been linked to Necrotizing Autoimmune Myopathy. We retrospectively analyzed patients positive for anti-HMGCR from 2014 to 2017.

Method

Anti-HMGCR were tested by either line-blot (Research. Euroimmun®), home-made immunoblot (Sant Pau), ELISA (INOVA®) and dot-blot (Dtek®). Further studies included: ANA screening (Bioplex2200), Myositis antibodies (Euroimmun4G), IIF in rat kidney/stomach/liver (1/160) and Hep2 (1/80) -INOVA-. Detailed clinical and laboratory data, EMG, MR and biopsy were recorded when available.

Results

12 Patients were positive for anti-HMGCR. Mean age at diagnosis was 68±9 years. Women:men ratio 5:7. All patients had been exposed to statins (92%>12 months). Symptomatic patients (83%) showed: symmetric weakness (90%), myalgia (90%), dysphagia (40%) and dyspnea (50%). CK levels [mean: 4743 U/L range 1416-14959], Aldolase [45.17 U/L (10,63-149,05)], transaminases, LDH were elevated at debut. Liver IIF pattern described for anti-HMGCR (HALIP) was positive in 11 patients. Hep2 cytoplasmic granular pattern was suspected in 6 of them. 2 patients presented Myastenia Gravis with anti-AchR. Muscle biopsies showed necrosis (50%), myophagia (66%), regeneration (66%) and absent or mild lymphocytic inflammation (66%). When available, MR and EMG were altered in 83% and 54%, respectively. Statins withdrawal was insufficient in 9 patients who required immunosupression. Clinical and CK relapse was concomitant in 2 of 3 patients who had previously achieved clinical remission.

Conclusion

The diverse clinical and laboratory features described herein makes anti-HMGCR the hallmark of this entity. High concordance between anti-HMGCR and HALIP supports the usefulness of tissue IIF as a screening tool.Our results suggest the value of analytical follow-up in monitoring response to treatment.

AUTO1-0859
SHORT ORAL DISCUSSION 14 - THYROID AUTOIMMUNITY (STATION 2)

POLYMORPHISMS OF PROMOTER GENE FORKHEAD BOX PROTEIN-3 (FOXP3) T-REGULATOR IN PATIENTS WITH GRAVES' DISEASE IN WEST SUMATRA, INDONESIA

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Background

Forkhead Box Protein 3 (FOXP3) is a gene that controls the development and function of T-regulatory (Treg) cells. Dysfunction of Treg cells can trigger an autoimmune condition caused by a change in FOXP3 promoter gene activity. Aim of this study is to correlate between FOXP3 T-regulator promoter gene polymorphisms in patients with Graves' disease in West Sumatera, Indonesia.

Method

This study was an observational study with cross sectional comparative study design. Consecutive sampling was conducted in patients with Graves' disease who came to outpatient clinic and treated in Dr. M. Djamil Hospital, Padang. Blood sampling was performed on 30 Graves' subjects and 30 healthy control subjects based on inclusion and exclusion criteria. DNA isolation, primary construction, polymorphism identification were analyzed by PCR method.

Results

Results of this study obtained the most age of patients with Graves' disease is 30-40 years with female gender. Graves' patient group was found to have SNP rs2232365, SNP rs3761547, SNP rs3761548 and SNP rs3761549 with mutan heterozygote polymorphisms were mostly found, and there was no polymorphism of SNP rs2232364 found in patients with Graves' disease on this study. There was no correlation between polymorphisms of promotor gene FOXP3 in Graves' disease group and healthy control group.

Conclusion

This study proves that there are polymorphisms of promoter gene FOXP3 in patients with Graves' disease, however there is no correlation between polymorphisms FOXP3 promoter gene in Graves' disease compare to control.

AUTO1-1000
SHORT ORAL DISCUSSION 14 - THYROID AUTOIMMUNITY (STATION 2)

THE CO-OCCURENCE OF AUTOIMMUNE THYROIDITIS AND PRIMARY SJOGREN'S SYNDROME - NOT A COINCIDENCE?

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Background

Primary Sjogren's syndrome (pSS) is an autoimmune disease characterized by lacrimal and salivary gland involvement. Other autoimmune disorders are frequent in pSS patients and autoimmune thyroiditis (AT) is one of the most prevalent. Both pSS and AT are more common in middle age women and therefore their co-occurrence may not be a coincidence.To evaluate the prevalence of AT in pSS patients and to compare it to the prevalence in the world population (1-2%) and to characterize and compare pSS patients with and without AT.

Method

Twenty-five pSS patients followed in our hospital were recruited. All fulfilled the classification criteria of the American-European Consensus Group for pSS. AT was defined as the association of positive anti-TPO and/or anti-TG antibodies with heterogeneity in thyroidal parenchyma at ultrasound evaluation.

Results

The population included 25 women, mean age 57.2±13 (SD) years. 24% of pSS patients had thyroid disease (N 6/25): 3 patients (12%) had AT and 3 (12%) had goiter. In 2 patients, AT was diagnosed before pSS and in 1, after. Patients with isolated pSS had more arthralgia/arthritis (p-value 0.0001) and therefore hydroxychloroquine was more prescribed (p-value 0.0234); patients with pSS and AT had more xerostomia and xerophthalmia (p-value of 0.0006 and 0.077, respectively), hypergammaglobulinemia (p-value 0.004), positive SS-A antibody, namely anti-roR52 (p-value 0.001) and rheumatoid factor (p-value 0.0001).

Conclusion

The main limitation of this study is the small number of patients. Still, AT seems more frequent in pSS patients and some clinical and laboratory differences may exist in pSS patients with and without AT.

AUTO1-1003
SHORT ORAL DISCUSSION 14 - THYROID AUTOIMMUNITY (STATION 2)

GENETIC VARIATION IN NFE2L2 AND SEPS1S ASSOCIATED WITH INCREASED RISK OF HASHIMOTO'S THYROIDITIS

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Background

Hashimoto's thyroiditis (HT) is the most common chronic autoimmune thyroid disease, which is characterized by alteration of the thyroid function. HT is a multifactorial disorder and several candidate genetic loci have been identified as contributing to HT. The transcription factor Nrf2, encoded by the NFE2L2 gene, is an important regulator of the cellular protection against oxidative stress. The relevance of selenoproteins in follicular thyroid cell physiology and in molecular physiology have pointed to a putative role of the interaction of Nrf2 with selenoproteins in the pathogenesis of autoimmune thyroid diseases.

Method

In order to evaluate the role of a promoter variation in *NRF2 and SEPS1* in the risk for developing Hashimoto's thyroiditis (HT), we performed a case-control study comprising 997 individuals (HT patients and unrelated controls).Genetic variants were discriminated by real-time PCR using TaqMan SNP genotyping assays.

Results

Three polymorphisms (– 653A/G : rs35652124; – 651G/A: rs6706649 and – 617C/A: rs6721961 SNPs) in the NRF2 gene promoter were studied and no significant difference were found between HT patients and controls with regard to genotypic or allelic frequencies of the three NFE2L2 SNPs ($P > 0.05$). The joint effect of genetic polymorphisms in NFE2L2 and SEPS1 was assessed considering the high-risk genotypes of *NF2L2 and SEPS1.*

Conclusion

Our findings suggest that the risk to develop Hashimoto's thyroiditis is not associate to a single NFE2L2 polymorphisms but increases with the combined effect of the number of risk alleles in *NFE2L2* and *SEPS1*. Individuals carrying two high-risk genotypes present a significant increased risk for HT.

AUTO1-0553
SHORT ORAL DISCUSSION 14 - THYROID AUTOIMMUNITY (STATION 2)

TYPE 1 DIABETES AND THYROID AUTOIMMUNITY IN PEDIATRICS: A CASE REPORT

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Background

Type 1 diabetes(DM1), an autoimmune disease, is the most common type of diabetes in children and adolescents. It is also the most common chronic disease in children in the developed countries. Annually an estimation of 65,000 children develop the disease and its incidence is increasing.

Method

It is defined by one or more autoimmune markers, including islet cell autoantibodies (ICA), autoantibodies to insulin (IAA), GAD (GAD65), the tyrosine phosphatases IA-2 and IA-2b. The disease has strong HLA associations, with linkage to the DQA and DQB genes.

Results

We present a case of a 11-year-old girl, diagnosed for DM1 since she was 6 years old. Last year, a TSH screening revealed subclinical hypothyroidism (TSH < 0,01 mUI/L) with AAT > 3000 UI/ml. The HLA haplotype was HLA DR4- DQ8, and at time for thyroid dysfunction diagnosis, glycemic control was poor, with haemoglobin A1C of 10,5% (median estimated glycaemia 255 mg/dl). She is now being monitored for celiac disease serology markers and has presenting signs of PDAH. She is on a multidisciplinary outpatient consult.

Conclusion

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes. At the time of diagnosis, about 25% of children with type 1 diabetes have thyroid autoantibodies. Patients with type 1 diabetes should be screened for autoimmune thyroid disease at diabetes diagnosis. Measuring thyroid autoantibodies (anti-thyroid peroxidase [TPO] and anti-thyroglobulin [TG]) identifies patients at increased risk for thyroid autoimmunity.

AUTO1-0023
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

READABILITY OF WIKIPEDIA PAGES ON AUTOIMMUNE DISORDERS: SYSTEMATIC QUANTITATIVE ASSESSMENT

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Background

recently published patient surveys of people with autoimmune disorders confirmed that the Internet was reported as one of the most important health information sources. Wikipedia, a free online encyclopedia launched in 2001, is generally one of the most visited websites worldwide and is often consulted for health-related information.

Method

We analyzed Wikipedia articles for their overall level of readability with 6 different quantitative readability scales: (1) the Flesch Reading Ease, (2) the Gunning Fog Index, (3) the Coleman-Liau Index, (4) the Flesch-Kincaid Grade Level, (5) the Automated Readability Index (ARI), and (6) the Simple Measure of Gobbledygook (SMOG). we investigated the correlation between readability and clinical, pathological, and epidemiological parameters. each Wikipedia analysis was assessed according to its content, breaking down the readability indices by main topic of each part

Results

134 diseases from the AARDA website. The Flesch Reading Ease yielded a mean score of 24.34 , indicating that the sites were very difficult to read and best understood by university graduates, while mean Gunning Fog Index and ARI scores were 16.87 and 14.06, respectively. The Coleman-Liau Index and the Flesch-Kincaid Grade Level yielded mean scores of 14.48 and 14.86 , respectively, while the mean SMOG score was 15.38. All the indices confirmed that the sites were suitable for a university level. no correlation between readability and clinical, pathological, and epidemiological parameters.

Conclusion

Wikipedia related to a low level of readability. The onus is to improve the health skills of patients and to create readable sites, in terms of clarity and conciseness.

AUTO1-0966
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

COMPARINGTHE HELIOS AUTOMATED IMMUNOFLUORESCENCE SYSTEM TO MANUAL PROCESSING AND READING FOR ANCA DETERMINATIONS

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Background

Anti-neutrophil cytoplasmic antibody (ANCA) testing is performed by labor intensive immunofluorescence (IFA). The AESKU HELIOS instrument automates the IFA procedure and reading/interpretation processes. We compared the HELIOS to manual IFA for ANCA testing in a large community teaching hospital.

Method

We analyzed 135 specimens from patients with autoimmune associated vasculitis, 120 from patients with documented ANCA and 375 from patients with other diseases. All 630 specimens were tested on ethanol and formalin fixed neutrophils by three different methods.

Method A- Automated Slide processing and automated interpretation on the HELIOS.

Method B- Automated slide processing on the HELIOS; manual reading of the image on the computer by 2 independent, experienced readers

Method C- Manual slide processing and microscopic evaluation by the readers.

Results

On ethanol fixed slides overall positive and negative agreement of all method comparisons and both readers ranged from 89.4-96.8%. Pattern agreements for all comparisons and readers ranged from 77.8-89.2% with the highest agreements between methods B and C; both methods of which relied on manual interpretation. On formalin fixed slides, overall positive and negative agreement between all methods and both readers ranged from 77.6-95.9%. Pattern agreements for all comparisons and readers ranged from 69.7-90.8% with the highest agreements between methods A and B.

Conclusion

The HELIOS automated slide processor/reader provides qualitative results similar to manual processing and reading for ANCA. Review of the HELIOS interpretations by a trained reader will ensure that appropriate patient results are reported.

AUTO1-0967
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

COMPARINGTHE HELIOS AUTOMATED IMMUNOFLUORESCENCE SYSTEM TO MANUAL PROCESSING AND READING FOR ANTI-DNA DETERMINATIONS

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Background

Anti-double stranded DNA antibody (anti-DNA) testing are often performed by labor intensive immunofluorescence (IFA). The AESKU HELIOS instrument automates the IFA procedure and reading. We compared the HELIOS to manual IFA for anti DNA testing in a large community teaching hospital.

Method

We analyzed 297 specimens from patients with SLE and 479 from patients with other diseases. All 776 specimens were tested on *Crithidia lucliae* slides at a 1:10 dilution by three different methods.

Method A- Automated Slide processing and automated interpretation on the HELIOS.

Method B- Automated slide processing on the HELIOS; manual reading of the image on the computer by 2 independent, experienced readers

Method C- Manual slide processing and microscopic evaluation by the readers.

Results

Overall agreements between all methods and both readers ranged from 80.3.7-97.5%, Positive agreements for all comparisons ranged from 44.8-91% and negative agreements were 83.9-98.3%. The highest agreements were between methods B and C; both methods of which relied on manual interpretation.

Conclusion

No subjective difference was found between slides prepared manually and slides prepared on the automated HELIOS platform. The HELIOS automated slide processor/reader provided results similar to manual processing and reading for anti-DNA assays. Review of the HELIOS interpretations by a trained reader will ensure that appropriate patient results are reported.

AUTO1-0279
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

ZENIT-PRO, A FULLY AUTOMATED INDIRECT IMMUNE FLUORESCENCE ANALYSER: A PRELIMINARY EVALUATION OF THE ANALYTICAL PERFORMANCE.

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Background

The newly developed Zenit-PRO system (A.Menarini Diagnostics) is a fully automated instrument performing IIF assays that streamlines the complete IIF protocol, from slide processing to reading and interpretation of results. This study was aimed to make a preliminary evaluation of Zenit-PRO ANA testing by IIF on HEp2 cells on a series of samples to set the negative/positive cut-off, to evaluate operating modes, execution times and analytical performance (repeatability, titrations).

Method

We selected 64 ANA positive patients with nuclear or cytoplasmic patterns at different titres (from 1:80 to >1:5120); 31 ANA-negative patients and 50 age/sex matched blood donors (BDs). We made three complete sessions on three different days and eight positive samples were chosen for between-run and within-run repeatability tests and titrations. The Zenit-PRO expresses the positivity score in % (0 to 100% of the sensor saturation).

Results

Overall, ANA positive samples disclosed higher scores than samples from BDs ($p<0.0001$) and ANA negative samples ($p<0.0001$). By ROC curve analysis we identified a negative cut-off <25% (sensitivity 85%, specificity 88%, LR 5.8), a grey zone between 25-35% and a positive cut-off >35% (sensitivity 70%, specificity 94%, LR+ 3). Between-run and within-run repeatability tests revealed mean CV around 10-15% and titrations run very well for all the different patterns.

Conclusion

The Zenit-PRO showed good agreement with manual and in-house automatic methods and pretty good analytical performance. The consolidation of the here identified negative/positive cut-offs is ongoing using larger series as well as the optimization of the software for pattern recognition and other IIF substrate automatic analyses.

AUTO1-0923
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

ARE NEUTRALIZING AUTOANTIBODIES TO INFLIXIMAB AND TOCILIZUMAB THE MAIN REASON OF THE SECONDARY NON-RESPONSES IN RHEUMATOID ARTHRITIS PATIENTS? DATA FROM THE RUSSIAN NORTH-WESTERN BIOLOGICAL TREATMENT COHORT

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Biologics are drugs that dramatically improved the status of rheumatoid arthritis (RA) patients. At the same time secondary inefficacy is one of the most important problems of biological therapy in daily clinical practice. The place of neutralizing antibodies in secondary non-efficacy is unknown.
The aim of the study was to evaluate the number of patients with rheumatoid arthritis with presence of the neutralizing autoantibodies to tocilizumab or infliximab at weeks 24 and 72 and their interrelations with the number of treatment non-responders in the same time-points.

Methods. Analysis of the data from 97 patients with rheumatoid arthritis, fulfilled EULAR2010 criteria, from North-Western Biological treatment Cohort Study (St. Petersburg, Russia) was performed. 54 patients with infliximab and 43 patients on tocilizumab treatment were involved. Number of the patients with presence of neutralizing antibodies was calculated. For the evaluation of neutralizing autoantibodies in sera we used the standard enzyme immunoassay. The DAS28 and high-sensitive C-reactive protein (C-RP) were collected as markers of RA activity. Treatment response was measured due to EULAR guidelines.The approval of the local ethics committee was obtained.

Results. Disease activity, demographic characteristics, and concomitant treatment (including methotrexate, glucocorticoids, NSAIDs, analgesics) in RA patients at baseline were similar in the treatment groups ($p \geq 0.05$ for all the parameters). There was no difference in the response (DAS28 and C-RP) and number of secondary non-responders at weeks 24 and 72 in infliximab and tocilizumab treatment groups. Number of secondary non-responders at weeks 24 and 72 was 11.1 and 9.3 % in infliximab and tocilizumab treatment, respectively, $p \geq 0.05$. Interestingly, that in the same time tocilizumab neutralizing antibodies were produced statistically less, than infliximab autoantibodies ($p=0.001$).

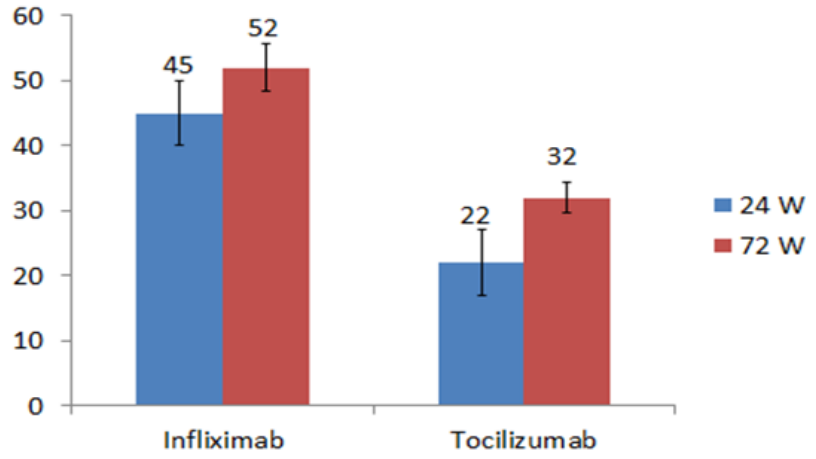

Fig. 1.The percentage of patients with rheumatoid arthritis with formation of neutralizing autoantibodies to infliximab and tocilizumab (%), n = 97.

Conclusions. According to the real-world data from the North-Western Biological treatment Cohort, in patients with rheumatoid arthritis, treated with infliximab, the neutralizing autoantibodies were produced frequently, than in RA patients, treated with tocilizumab. Taking into account the similar treatment response and similar secondary non-response in infliximab and tocilizumab treatment groups, the place of neutralizing autoantibodies in development of secondary non-efficacy remains unclear.

AUTO1-0498
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

IMPROVED ANTI-NUCLEAR ANTIBODY (ANA) SCREENING USING A NOVEL HEP2 SUBSTRATE

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Background

Accurate interpretation of DFS70 (dense fine speckled 70) and mixed ANA patterns can be challenging using conventional HEp-2. We evaluated a novel IIF HEp-2 ELITE/DFS70-KO substrate composed of PSIP1/LEDGF/DFS70knockout Hep-2 and its utility in improving the interpretation of DFS pattern during the ANA screening step along with simultaneous confirmation of anti-DFS70 antibodies.

Method

1005 consecutive routine ANA screening samples were screened at 1:80 using conventional HEp-2 and HEp-2 DFS70 KO substrates (Immuglo ANA-HEp-2 and HEp-2 ELITE/DFS70-KO, Trinity Biotech, Buffalo, NY). Anti-DFS70 antibody specificity was determined by immunoblot (IB) (Euroimmune AG, Luebeck, Germany). Clinical and serological data were included in analyzing the overall impact of the novel HEp-2 DFS70-KO substrate on DFS pattern interpretation.

Results

Twenty-two out of the 1005 samples tested were selected as positive for anti-DFS70 antibodies by IB and/ or suspected as DFS pattern by ANA screen using two HEp-2 substrates (Table 1). Of these 22 cases suspected as DFS alone or in combination with homogeneous or speckled patterns on conventional HEp-2, 17 were interpreted as positive for DFS70 (monospecific DFS70 (10), mixed DFS70 (7)), speckled (3) and DFS (2) patterns by new HEp-2 DFS70 KO substrate (Fig 1). HEp-2 DFS70 KO substrate was not only useful in decrypting unclear mixed patterns (Fig 1) but also highly sensitive for DFS70 relative to IB (Cohen’s kappa, 0.338; Fig. 2).

Table1: Clinical and serological analysis of 22 DFS pattern suspect cases

Sample #	ANA Pattern on conventional HEp-2	ANA Pattern on HEp-2 DFS70 KO	Anti-ENA and anti-dsDNA by Bio-Plex2200	ANA Profile by IB	AARD association
1	DFS	**DFS70**	Neg	DFS70, Histone	No
2	DFS/S	S+DFS70	SSA60	SSA60, dsDNA (+/-)	Yes
3	DFS/H/S	S+DFS70	SSA60	DFS70	No
4	DFS/H/S	**DFS70**	Neg	Neg	No
5	DFS/H	**DFS70**	Neg	Neg	No
6	DFS/S	S	SSA60, SSA52	SSA60, SSA52	Yes
7	DFS/S	**DFS70**	Neg	Neg	No
8	DFS	DFS	Neg	Neg	No
9	DFS/H/S	S+DFS70	SSA60, SSB	SSA60, SSA52, SSB, DFS70	Yes
10	DFS/S	S	Neg	Neg	No
11	DFS/S	**DFS70**	Neg	Neg	No
12	DFS/S	S+DFS70	Neg	Neg	No
13	DFS	**DFS70**	Neg	DFS70	No
14	DFS	**DFS70**	Neg	DFS70	No
15	DFS/H/S	**DFS70**	Neg	DFS70	No
16	DFS	S+DFS70	Neg	DFS70	No
17	DFS/H/S	S+DFS70	Neg	DFS70	No
18	DFS/H/S	**DFS70**	Neg	Neg	No
19	DFS	**DFS70**	Neg	DFS70	No
20	DFS/H/S	S	Neg	Neg	No
21	DFS/H/S	S+DFS70	Neg	Neg	No
22	DFS/H/S	DFS	Neg	Neg	No

Legend: HEp-2 DFS70 KO is a novel HEp-2 substrate with PSIP1/LEDGF/DFS70 knockout engineered cells mixed with conventional HEp-2 cells; IB (Immunoblot); ANA (Antinuclear antibodies); AARD (ANA associated rheumatic disease); DFS (Dense fine speckled), DFS70 (Dense fine speckled70), S (Speckled), H (Homogeneous) patterns.

Fig. 1: Interpretation of DFS suspect pattern by conventional HEp-2 and HEp-2 DFS70 KO substrates

Pattern on conventional HEp-2

Pattern on HEp-2 DFS70 KO

N=22	DFS	DFS/H	DFS/S	DFS/H/S
DFS	1	0	0	1
DFS70	4	1	2	3
DFS70+S	1	0	2	4
S	0	0	2	1

Fig. 2: Concordance between HEp-2 DFS70 KO method and IB

Anti-DFS70 antibodies positive by HEp-2 DFS70 KO

Anti-DFS70 antibodies by IB

N=22	Positive	Negative
Positive	9	0
Negative	8	5
Cohen's Kappa	0.338	

Conclusion

Novel HEp-2 ELITE/DFS70-KO substrate allows accurate interpretation of ANA pattern by distinguishing mixed and mono-specific DFS70 reactions with improved confidence while screening for disease associated ANAs.

AUTO1-0865
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

THE STUDY OF ASTHMA AMONG PATIENTS WITH RHEUMATOID ARTHRITIS (RA) PATIENTS.

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Background

Objectives:

Asthma and rheumatoid arthritis (RA) are two common diseases that are increasing in the world. To investigate whether is there any concerning to develop asthma in RA patients, this cross sectional study was designed to determine the relation between asthma and RA.

Method

We undertook a cross sectional study in two hospitals of Zahedan-Iran city from outpatients of immunology and allergy clinics .The study population consisted of 731 patients with asthma diseases during 2005-2016 that their diagnose was based on medical history, clinical and paraclinical examination. Patients completed a questionnaire form about personal data and underwent measuring IgG, IgA, IgM and total IgE serum. Among of these patients 327 of them had joint pain and suffered from some symptoms of rheumatoid arthritis diseases.

Results

From 426 asthma patients aged 23-78 years old with the mean age of 55, there were 40% females and 60% males. High level of serum immunoglobins especially total IgE were observed in 81% patients. From 327 RA patients aged 31-73 years old with the mean age of 52, there were 66% females and 34% males. High level of serum immunoglobins especially total IgE were observed in 78% patients.

Conclusion

A significant relation was found between the serum total IgE in patients with both asthma and rheumatoid arthritis.

AUTO1-0917
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

FUNCTIONAL DIAGNOSTICS FOR THYROTROPIN HORMONE RECEPTOR AUTOANTIBODIES: BIOASSAYS PREVAIL OVER BINDING ASSAYS

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Background

Autoantibodies to the thyrotropin hormone receptor (TSH-R) are directly responsible for the hyperthyroidism in Graves' disease and mediate orbital manifestations in Graves' orbitopathy. These autoantibodies are heterogeneous in their function and collectively referred to as TRAbs.

Method

Measurement of TRAbs is clinically important for diagnosis of a variety of conditions and different commercial assays with high sensitivity and specificity are available for diagnostic purposes. TRAbs detected in binding assays by mainly the automated electrochemical luminescence immunoassays (ECLIA) do not distinguish TRAbs that stimulate the TSH-R (called TSIs or TSAbs) and TRAbs that just inhibit the binding of TSH without stimulating the TSH-R (called TBAbs). However, TSAbs and TBAbs have divergent pathogenic roles,and depending which fraction predominates cause different clinical symptoms and engender different therapeutic regimen.

Results

This review aims to present a technical and analytical account of leading commercial diagnostic methods of anti-TSH-R antibodies, a metaanalysis of their clinical performance and a perspective for the use of cell based TSH-R bioassays in the clinical diagnostics of Graves' disease.

Conclusion

Diagnostic distinction of TSAbs and TBAbs is of paramount clinical importance. To date, only bioassays such as the Mc4 TSH-R bioassay (Thyretain™, Quidel) and the Bridge assay (Immulite 2000, Siemens) can measure TSAbs, with only the former being able to distinguish between TSAbs and TBAbs. On this note, it is strongly recommended to only use the term TSI or TSAb when reporting the results of bioassays, whereas the results of automated TRAb binding assays should be reported as TRAbs (of undetermined functional significance).

AUTO1-0235
SHORT ORAL DISCUSSION 15 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 1)

COMPARATIVE STUDY OF SAMPLES ANALYZED BY INMUNOBLOT, ELISA AND INDIRECT IMMUNOFLUORESCENCE ASSAY TECHNIQUES FOR ANTI-CENTROMER ANTIBODIES IN PATIENS WITH SUSPECTED AUTOIMMUNE DISEASE IN THE COMPENSAR

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Background

Indirect immunofluorescence Assay (IFA) has long been an ally at the time of contributing to the diagnosis of autoimmune diseases. This research seeks to compare IFA with ELISA and INMUNOBLOT techniques for the determination of anti-centromere antibodies in patients who have not yet been diagnosed with autoimmune disease at the COMPENSAR

Method

For this, the orders with anti-Centromere antibody request were processed simultaneously by the IFA, ELISA and INMUNOBLOT techniques and the results were compared, finding that their positivity or negativity is the same for the three techniques, verifying the great specificity of the immunofluorescence. For this, the reagents of the commercial house AESKU.DIAGNOSTIC ® were used

Results

The total samples of the patients were analyzed by IFA, IB and ELISA. This was done using the ANA Hep-2 kit from the AESKU commercial house on the HELIOS platform. Samples that were positive for anti-centromere antibodies by IFA without specific request for remission for anti-centromere were evaluated with Immunoblot using ANA-17pro. Finally, a comparison was made between immunofluorescence techniques against ELISA for the same number of samples using the Cenp-B kit, demonstrating once again that the positive samples for the anti-centromere standard were positive in the detection of the Cenp-B antigen specific.

Table 2. Kappa coefficients

	Cohen´S kappa		
	IFA Rem	*INMUNOBLOT*	*ELISA*
IFA	1	0.813	0.833
Fleiss´kappa		0.914	

Conclusion Immunoblot, ELISA and IFA, have shown us a great similarity in their results without one technique excluding the other, only that when distributing the economic resources better we would find in the ANA a response that will also ensure that the patient receives a correct diagnosis

AUTO1-0983
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

AUTOANTIBODY PROFILING IN LUPUS PATIENTS USING SYNTHETIC NUCLEIC ACIDS

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Background

Autoantibodies to nuclear components of cells (antinuclear antibodies, ANA), including DNA (a-DNA), are widely used in the diagnosis and subtyping of certain autoimmune diseases, including systemic lupus erythematosus (SLE). Despite clinical use over decades, precise, reproducible measurement of a-DNA titers remains difficult, likely due to the substantial sequence and length heterogeneity of DNA purified from natural sources.

Method

We designed and tested a panel of synthetic nucleic acid molecules composed of native deoxyribonucleotide units to measure a-DNA. ELISA assays using these antigens were applied to the cohort of 364 patient samples and 60 controls.

Results

The conducted assays show specificity and reproducibility. Applying the ELISA tests to serological studies of pediatric and adult SLE, we identified novel clinical correlations. We also observed preferential recognition of a specific synthetic antigen by antibodies in SLE sera. We determined the probable basis for this finding using computational analyses, providing valuable structural information for future development of DNA antigens.

Conclusion

Overall, synthetic antigens demonstrate high specificity, sensitivity and reproducibility in detection of a-DNAs in SLE, a disease known to be associated with a-DNAs, and for the first time enable a detailed structural study of sequence specificity of these autoantibodies. Other important advantages of the new synthetic antigens compared to natural heterogeneous molecules are: 1) Known specificity, including easily controlled sequence-specific binding of a-DNA antibodies; 2) Potential to determine individual antibody profiles which may have clinical implications; and 3) Potential to determine the biological role of a-DNA in SLE.

AUTO1-0862
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

DO CHILDREN WITH RHEUMATOLOGICAL DISEASES AT CARDIOVASCULAR RISK ?

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Background

Background

This study was designed to evaluate Lipid profile in children with juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus(SLE) and its relation to disease markers and treatment modalities for early identification and possible intervention to reduce cardiovascular risk .

Method

We measured Lipid profile (cholesterol, triglycerides, HDL and LDL) Erythrocyte Sedimentation rate (ESR) and C-reactive protein (CRP) to15 patients with JRA (group 1) and 15 patients with SLE(group 2) , we also assessed Disease Activity index and Carotid intimal media thickness(CIMT) for them.

Results

According to our results of lipid profile there were no statistically significant difference between group 1 and group 3 in TC , TG ,LDL and HDL, but there were high statistically significant difference between group 2 and group 3 in TC , TG ,LDL ($p<0.001$) and in HDL ($p<0.008$) .

positive significant correlations between DAI in group 1 with TC ($r=0.633$, $p=0.011$), TG ($r=0.523$, $p=0.046$) and LDL ($r=0.548$, $p=0.034$) .Also, positive significant correlations between DAI in group 2 with TC ($r=0.579$, $p=0.024$), TG ($r=0.559$, $p=0.030$) and LDL ($r=0.533$, $p=0.041$) .

Conclusion

Children with rheumatologic diseases are at high risks of cardiovascular events, so continuous monitoring of lipid profile can decrease mortality and co-morbidity.

AUTO1-0829
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

SYSTEMIC LUPUS ERYTHEMATOSUS WITH ANTI-DFS70 ANTIBODIES

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Background

Anti-DFS70 antibodies are found in 3% of general population. Isolated anti-DFS70 reactivity i.e. without anti-extractable nuclear antigens (anti-ENA) or anti-double stranded DNA (anti-dsDNA) has been proposed as an exclusion marker for systemic autoimmune rheumatic diseases. However, anti-DFS70 antibodies can be found in patients with systemic lupus erythematosus (SLE). Such patients have not been described yet.

Method

Fifty-nine SLE patients followed-up at the internal medicine department 2 at the Pitié-Salpêtrière hospital presenting with at least 4 ACR97 or SLICC2012 classification criteria and positive for anti-DFS70 antibodies were included and separated in 2 groups: (1) *isolated DFS group* (n=31) with isolated anti-DFS70 antibodies and (2) *DFS ENA/DNA group* (n=28) with anti-DFS70 and anti-ENA and/or anti-dsDNA antibodies. Presence of anti-ENA and anti-DFS70 antibodies were confirmed using the Maverick™ Detection System (Genalyte, Inc. USA).

Results

Among the 1200 SLE patients of the active file of the department, the anti-DFS70 positive patients represented 4.8% (n=59). The female/male sex ratio was 19/1, the average age at diagnosis 33 years, mean disease duration 6 years and mean follow up was of 4 years. There was no significant difference between the 2 groups in terms of clinical profile, number of flares, treatment or anti-DFS70 titer. The isolated DFS group presented less renal involvement (n=2, 6%) compared to the DFS ENA/DNA group (n=7, 25%, p=0.07).

Conclusion

SLE patients with isolated anti-DFS antibodies have a clinical phenotype comparable to the one of patients with anti-DFS antibodies associated with SLE antibodies. Diagnosis of SLE cannot be excluded in the presence of isolated Anti-DFS70 antibodies.

AUTO1-0962
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

THE NOVEL ANTI-CD40 MONOCLONAL ANTIBODY CFZ533 SHOWS BENEFICIAL EFFECTS IN PATIENTS WITH PRIMARY SJÖGREN'S `S SYNDROME

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Background

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by exocrine gland inflammation, secretory gland dysfunction, and frequent extra-glandular manifestations. The pathology of pSS has been linked to B cell hyper-reactivity, manifest as germinal center-like structures in salivary glands. As CD40-CD154 interactions are essential for germinal center formation, we sought to investigate the role of this pathway in pSS.

Method

To address the role of CD40-CD154 pathway blockade in the clinic, we developed CFZ533, a blocking, non-depleting anti-CD40 monoclonal antibody. We conducted a randomized, double–blind, placebo-controlled, Phase IIa study to evaluate the safety, and efficacy of CFZ533 in patients with pSS. Forty-four clinically active pSS patients were randomized to receive high or low dose CFZ533 or placebo over 12 weeks. Key outcomes included safety and efficacy as assessed by change in EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), measurements of pharmacokinetics and pharmacodynamics (PK/PD) of CFZ533, as well as other clinical outcomes and candidate biomarkers.

Results

Overall, CFZ533 was safe and well tolerated, and the majority of AEs were mild or moderate. We observed a five point reduction in ESSDAI in the high dose CFZ533 group compared to a drop of approximately 1 in the placebo group. Improvements in other measures including ESSPRI, and decreases in the germinal center-related serum biomarker CXCL13 were also observed in the high dose group.

Conclusion

Our data point to a pivotal role of CD40-CD154 interactions in pSS pathology and indicate, for the first time, that CD40 blockade has clinical benefit in patients suffering this autoimmune exocrinopathy.

AUTO1-0321
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

ANNEXIN A2 AND CARDIOVASCULAR CALCIFICATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Premature atherosclerosis is a major cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE). Cardiovascular disease and osteoporosis are linked by numerous factors, such as the RANK – RANKL – osteoprotegerin signalling pathway. Annexin A2 (ANXA2) stimulates osteoclastic precursors' differenciation through production of RANKL. We chose to study ANXA2 as a biomarker of cardiovascular calcification in SLE.

Method

We used a commercial ELISA sandwich kit to detect ANXA2 in 68 female lupus patients' sera. These patients had a screening for cardiovascular calcification, bone mineral density, and several bone turnover biomarkers (such as RANKL, osteoprotegerin, fetuin A) in a previous study. We investigated the correlation between ANXA2 and cardiovascular calcification, osteoporosis, and the bone turnover markers previously assessed.

Results

Serum median level of ANXA2 was 7,35 ng/ml [4,65-13,05]. Thirty patients had cardiovascular calcification ; 37 % had osteopenia, and 6 % had osteoporosis. ANXA2 was not correlated either with the presence or with the extent of cardiovascular calcification. There was a correlation between ANXA2 and femoral neck T-Score. Fetuin A was the only bone turnover biomarker to be correlated with ANXA2.

Conclusion

Abdel-Wahab *et al. (Arab J Nephrol Transplant 2013)* suggested that fetuin A deficiency was involved in cardiovascular calcification in SLE patients. ANXA2 was correlated with fetuin A and femoral neck T-Score in our study, implying ANXA2 could have a protective role in cardiovascular calcification in SLE.

AUTO1-0950
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

ADJUVANT INDUCED ECTOPIC EXPRESSION OF MHC II ON GLANDULAR CELLS IS A PRESYMPTOMATIC FEATURE OF SSA-PEPTIDE INDUCED MOUSE MODEL OF PRIMARY SJÖGREN'S SYNDROME

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Background

Ectopic expression of MHC II molecules on glandular cells is a feature of primary Sjögren's syndrome (pSS). However, the cause of the ectopic expression of MHC II is unknown, and whether it play a role in the disease pathogenesis remain elusive.

Method

We determined presymptomatic events in a mouse model for pSS induced by immunization of Ro60_316-335 peptide emulsified in Titermax as adjuvant. We investigated the gene expression profiling of mouse lacrimal glands before the onset of disease.

Results

Our results showed that ectopic expression of MHC II molecules on glandular cells was an early presymptomatic event in this mouse model of pSS. The ectopic expression of MHC II molecules was induced by Titermax but not complete freund's adjuvant (CFA). Furthermore, immunization of Ro60_316-335 peptide emulsified in Titermax, but not in CFA, could induce the pSS-like disease in mice.

Conclusion

Therefore, this result suggests that ectopic expression of MHC II molecules on glandular cells is a presymptomatic feature of pSS, and such ectopic expression can be caused by environmental factors. In addition, this study also suggests a novel mechanism of adjuvant action in potentiating immune responses.

AUTO1-1012
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

SLE PRESENTING AS LIBMAN-SACKS ENDOCARDITIS AND DIFFUSE ALVEOLAR HEMORRHAGE IN A PATIENT WITH ANTIPHOSPHOLIPID SYNDROME TREATED SUCCESSFULLY WITH CORTICOSTEROIDS AND IVG

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Background

Endocarditis is more often due to infection rather than autoimmune disease.

Method

We present a 48 year old male with known primary antiphospholipid syndrome (APS), and a previous episode of myopericarditis, who was admitted for effort dyspnea, hemoptysis and intermittent chest pain.

Results

Physical examination revealed a new systolic heart murmur. Initial laboratory workup demonstrated mild thrombocytopenia and a very elevated erythrocyte sedimentation rate. Blood cultures, PCR and a serologic panel for fastidious organisms were all negative. Trans-thoracic echocardiograms (TTEs) followed by a trans-esophageal echocardiogram (TEE) demonstrated moderate-severe aortic regurgitation (AR), multiple vegetations on the aortic and mitral valves, suggestive of noninfectious endocarditis. A chest CT scan revealed bilateral alveolar opacities compatible with diffuse alveolar hemorrhage (DAH) and later confirmed by bronchoscopy. Autoimmune serology included a triple positive antiphospholipid (aPL) antibody profile and an elevated ANA titer. The diagnosis of SLE was confirmed by pulmonary and cardiac involvement, positive serology and secondary APS. Treatment with high dose oral prednisone (60 mg/day) and plaquenil was initiated. Sequential TTEs every 2 weeks demonstrated shrinking of the vegetations, and finally no vegetations were evident after 6 weeks of steroid treatment. Attaining remission of DAH and steroid-sparing required the initiation of high dose IVIG. The patient underwent successful aortic valve replacement for severe AR without post-operative complications.

Conclusion

This is a rare case of an APS patient with thrombotic endocarditis complicated by severe AR and DAH where SLE was then diagnosed. Treatment with systemic corticosteroids and high dose IVIG were beneficial.

AUTO1-0316
SHORT ORAL DISCUSSION 16 - SLE, SJÖGREN'S DISEASE (STATION 2)

MOROCCAN PATIENTS WIH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a high female predominance. Several genetic, immunological and environmental factors can lead to this disease.The present work studies the clinical and immunological features in a series of 50 Moroccan patients with SLE in University Hospital Center of Rabat-Morocco between December 2011 and December 2013.

Method

All patients were screened for antinuclear antibodies (ANA) and anti-DNA antibodies by indirect immunofluorescence, followed by identification of anti-extractable nuclear antigen (ENA) antibodies and anti-β2GP1 antibodies by ELISA.

Results

The female to male ratio was 6.1:1, with a mean age of 31.72 years. The main clinical characteristics were: arthritis (82%), mucocutaneous manifestations (80%), renal involvement (50%) and hematological abnormalities (46%). Of the mucocutaneous features, the highest frequencies were observed in the malar rash (68%) and photosensitivity (60%). Of the hematological features, lymphopenia was most frequently observed in 30% of patients, followed by hemolytic anemia in 16%, leucopenia and thrombocytopenia in 8%. Central nervous system was involved in 10%. ANA were found in 88%, anti-DNA antibodies in 56%, and anti-Sm antibodies in 50%. Anti-SSA, anti-SSB and anti-Sm/RNP antibodies were detected in 38%, 10% and 48%, respectively. Anti-Scl70 antibodies were reported in 8% and anti-β2GP1 in 14%.

Conclusion

Our findings are in agreement with other Arab studies and confirm that regardless of the geographical studied regions, the main clinical symptoms proposed by ACR and identified at the time of diagnosis remain comparable.

AUTO1-0919
SHORT ORAL DISCUSSION 17 - TYPE 1 DIABETES MELLITUS (STATION 1)

CLINICAL MANIFESTATIONS, SURVIVAL AND CAUSES OF DEATH OF PATIENTS WITH SLE IN SAIFUL ANWAR GENERAL HOSPITAL, MALANG, INDONESIA

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Background

The aim of the study was to analysed the clinical manifestations and survival of SLE patients in Saiful Anwar General Hospital, Malang, Indonesia.

Method

All medical records of SLE in Rheumato-Immunology Division of Saiful Anwar General Hospital from year 2013 to 2017 (640 medical records from 373 SLE patients) were studied . Survival analysis was analyzed using Kaplan-Meier and Life Table methods.

Results

The median age at the time the patient was diagnosed with SLE is 28 years. The median difference between the of age of onset and diagnosis was < 1 year. About 30% of patients were late to be counselled to Rheumatologist. 84.1% of patients showed disease remission, with the median period of first remission was 20 months. Many of the patients had fatigue (82%) , symptoms and signs of depression and/or anxiety (50%), leaving school (43%), and quit from work (32,5%). Lupus nephritis is a common manifestation , followed by haemolytic anemia, thrombocytopenia, lupus neuropsychiatric and serositis. Survival of SLE patients in Saiful Anwar General Hospital for 1 year is 88%, for 5 years is 80%, and for 10 years is 75%. The mortality rate of inpatient cases is 16.3%, with the cause of death was SLE activity (39.2%), infection (23.5%), and combination of SLE and infection (37.3%).

Conclusion

Survival of our patients for 1 year is 88%, for 5 years is 80%, and for 10 years is 75%. The causes of death are disease activity, infection and combination of both as causes of death

AUTO1-0959
SHORT ORAL DISCUSSION 17 - TYPE 1 DIABETES MELLITUS (STATION 1)

DETECTION OF AUTOREACTIVE CD8+ T CELLS IN TYPE 1 DIABETES BY BARCODED MHC CLASS I MULTIMERS

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Background

Recognition of self-antigens by autoreactive T cells leads to destruction of tissue in autoimmune diseases like Type 1 Diabetes (T1D). However, the exact recognition patterns leading to disease outbreak and progression have not been fully clarified. T1D is an autoimmune disease caused by T cell-mediated destruction of the pancreatic β-cells leading to insulin deficiency. Posttranslational modification (PTM) of peptides seems to contribute to breaking self-tolerance in autoimmune diseases. Citrullination, the deamination of arginine, of T1D autoantigens may play a major role in the initiation and progression of autoimmunity.

Method

We developed a technique that implements the MHC multimer-based detection of antigen-responsive T cells by unique DNA barcodes. It allows the simultaneous detection of >1000 $CD8^+$ T cell responses in one sample. Therefore, the barrier for high-throughput detection of antigen-responsive T cells has been removed.
To investigate the role of citrullination in the course of T1D, we *in silico* predicted peptides from the four major T1D autoantigens GAD65, Insulin, IA-2 and ZnT8 presented by HLA-A2, -A24, -B8 and -B15, all genetically linked to T1D.

Results

More than 800 peptides containing Arginine were predicted in its native and citrullinated form. HLA binding affinity was validated by HLA-affinity ELISA. We now aim to identify $CD8^+$ T cell responses in peripheral blood mononucleated cells from newly diagnosed T1D patients and healthy donors towards the selected peptides with barcoded MHC class I multimers.

Conclusion

Once the molecular mechanisms of autoreactivity have been elucidated, it becomes possible to specifically target CD8+ T cells and their antigens in T1D.

AUTO1-0243
SHORT ORAL DISCUSSION 17 - TYPE 1 DIABETES MELLITUS (STATION 1)

AUTOIMMUNITY AND ENDOCRINE DYSFUNCTION IN TYPE 1 DIABETES- REDEFINED IN INDIAN SUBCONTINENT

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Background

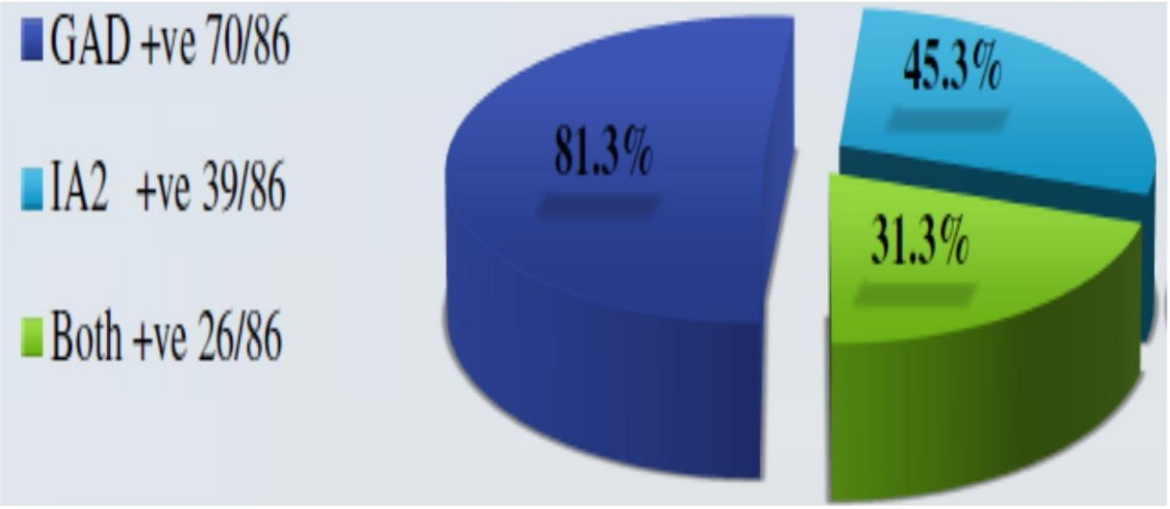
As per literature, majority of the Indian type 1 diabetic patients are 1b, as compared to the western population. The Commonest autoimmune disorders associated with Type 1 Diabetes mellitus are :Autoimmune thyroid disease and celiac disease.So the aims and objectives of our study was to study the autoimmune antibody profile of type 1 diabetic patients and to study the prevalence of other autoimmune disorders in type 1 diabetics.

Method

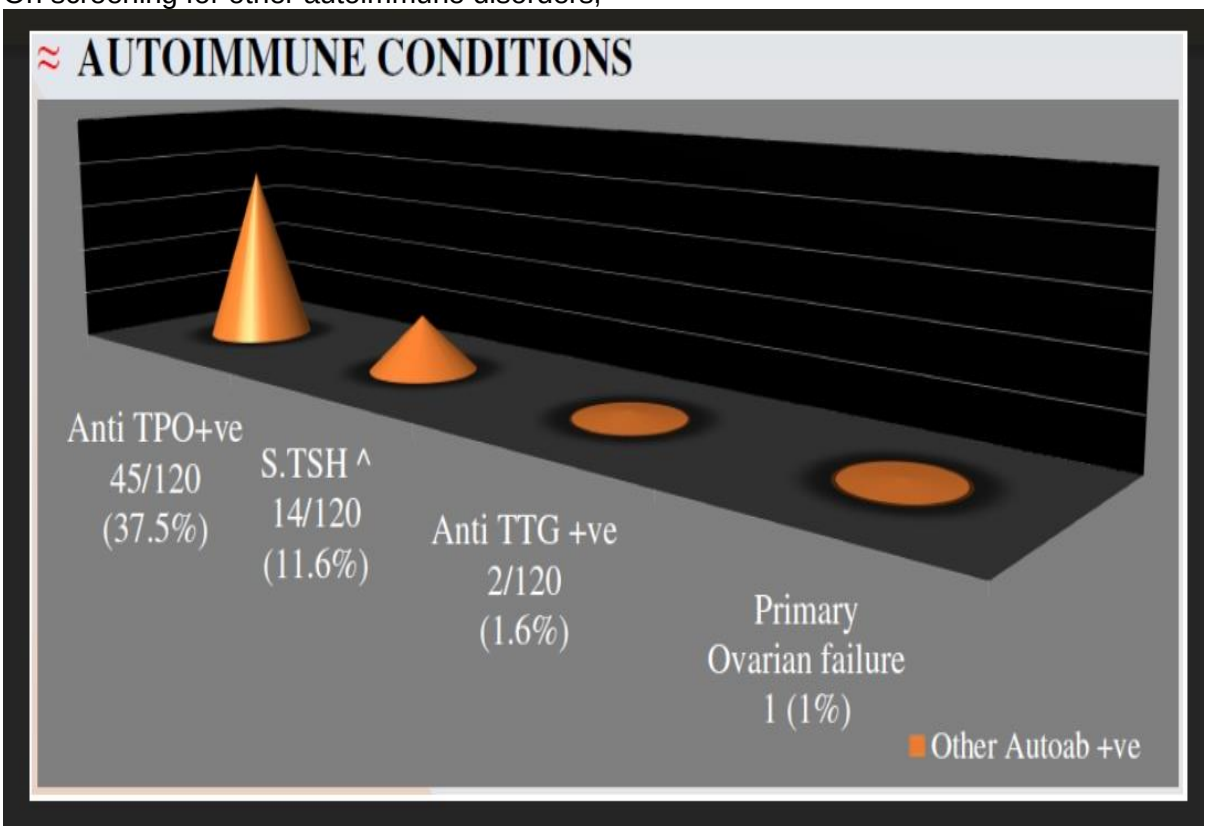
All 120 patients with clinical diagnosis of Type 1 diabetes underwent screening for auto antibodies- GAD 65 and IA2 as well as thyroid dysfunction & thyroid autoantibodies and Anti TTG antibody estimation was done in all patients to screen for celiac disease. In clinically indicated patients, ACTH stimulated cortisol levels, FSH, LH and testosterone or estrogen levels were done.

Results

Out of the total 120 patients studied,63 were males and 57 were females. The average age of presentation was 12.5 ± 3.5 years(Range: 2-21 years).



On screening for other autoimmune disorders,



Conclusion

Our study population is predominantly autoantibodies positive (1A),which is similar to the Caucasian population.This is contrary to what literature states , that majority of the Indian type 1 diabetic patients are antibody negative(1b) , as compared to the western population. Early screening for autoantibodies in work up of Type1DM can aid in its diagnosis as well as associated disorders & predict future risk .Thyroid disease still remains the most common autoimmune disorder in Type 1 DM. The incidence of celiac disease in the population studied is lesser than what is described in literature.

AUTO1-0839
SHORT ORAL DISCUSSION 17 - TYPE 1 DIABETES MELLITUS (STATION 1)

A PROTEIN-ENGINEERED MOLECULES CARRYING GAD65 EPITOPES AND TARGETING CR1 SELECTIVELY DOWN-MODULATES DISEASE-ASSOCIATED HUMAN B LYMPHOCYTES

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Background

Autoimmune Diabetes Mellitus (ADM) is an autoimmune metabolic disorder characterized by chronic hyperglycemia, the presence of autoreactive T and B cells and autoantibodies against self-antigens. A membrane bound enzyme on the pancreatic beta-cells, GAD 65, is the main autoantigen in ADM. Autoantibodies against GAD65 lead to beta-cells destruction and decline of pancreatic functions.

The human complement receptor type 1 (CR1) on B- and T-lymphocytes has a suppressive activity on these cells. We hypothesized that it may be possible to eliminate GAD65-specific B cells from ADM patients by using chimeric molecules, containing an anti-CR1 antibody, coupled to peptides resembling GAD65 B/T epitopes. These molecules are expected to bind selectively the anti-GAD65 specific B-cells by the co-crosslinking of the immunoglobulin receptor and CR1 and to deliver a suppressive signal.

Method

Two synthetic peptides derived from GAD65 protein (GAD65 epitopes), and anti-CD35 monoclonal antibody were used for the construction of two chimaeras (GAD65-1 and GAD65-2). The immunomodulatory activity of the engineered antibodies was tested *in vitro* (Epitopes prediction, Protein engineering, ELISA, FACS, ELISpot and Proliferation assays) using PBMCs from diabetic patients.

Results

A reduction the number of anti-GAD65 IgG antibody-secreting plasma cells and increased percentage of apoptotic B lymphocytes was observed after treatment of PBMCs from diabetic patients with engineered antibodies.

Conclusion

The constructed chimeric molecules are able to modulate selectively the activity of GAD65-specific B-lymphocytes and the production of anti-GAD65 IgG auto-antibodies by co-crosslinking of the inhibitory CR1 and the BCR. This treatment presents a possible way to alter the autoimmune nature of these cells.

AUTO1-1054
SHORT ORAL DISCUSSION 18 - VASCULITIDES, HORMONES AND AUTOIMMUNITY (STATION 2)

GIANT CELL ARTERITIS - CLINICAL FEATURES IN A PRIVATE UNIVERSITY HOSPITAL

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Background

Giant cell arteritis (GCA) is a large-vessel systemic vasculitis with chronic inflammation that predominantly (but not only) affects cranial aortic branches. Although temporal artery biopsy (TAB) remains the gold standard for the diagnosis of GCA, Color Doppler ultrasonography (CDUS) in skilled hands can be diagnostic. Glucocorticoids are the main treatment but adjunctive therapies are needed in resistant disease and to reduce the burden of corticosteroids.

Method

Medical records of all patients with large-vessel vasculitis followed in a private university hospital were assessed, since 2009. Demographic data, age at diagnosis, presenting symptoms, presence of TAB and image modalities, immunomodulatory therapy and concomitant polymyalgia rheumatica (PMR) were evaluated.

Results

We found 11 patients with GCA and the. mean age at diagnosis was 68 years old. The majorithy were female (64%, 7/11) and had systemic symptoms (73%, 8/11). Headache was common to all patients and 45% (4/11) had fever. Jaw claudication and amaurose fugax were rare symptoms (1%, 1/11). The TAB was diagnostic in 55% (6/11) of the patients and the halo sign was present in 50% of these patients. In 60% (3/5) of the remaining patients, there was halo sign in CDUS. In two patients the diagnosis was only clinical. Adjunctive immunomodulatory therapies were needed to control disease activity or for glucocorticoids sparing in 5/11 patients (azathioprine N=3, methotrexate N=1, cyclophosphamide N=1). Few patients (27%, 3/11) had PMR (one before and two after GCA diagnosis).

Conclusion

We assessed clinical features of GCA in a private university hospital. We found a halo sign sensitivity of 50%.

AUTO1-1044
SHORT ORAL DISCUSSION 18 - VASCULITIDES, HORMONES AND AUTOIMMUNITY (STATION 2)

CLINICAL AND LABORATORY CHARACTERISTICS OF ANCA - POSITIVE PATIENTS: RETROSPECTIVE ANALYSIS IN A GENERAL HOSPITAL

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Background

The anti-neutrophil cytoplasmic antibody (ANCA) - associated vasculitis is a group of rare heterogeneous diseases, that requires a structured clinical and laboratory approach. Application of ANCA testing as a clinical diagnostic tool is still controversial.
The objectives were to study the outcome, clinical and laboratory characteristics of ANCA positive patients.

Method

Retrospective analysis of the data of all patients with c-ANCA proteinase 3, p-ANCA Mieloperoxidase and atypical ANCA positive tests between 2008 and 2017, irrespective of the diagnosis.

Results

It were performed 3897 ANCA tests, 3% were positive. Sixty patients (32males/28females) were included, 21 c-ANCA, 30 p-ANCA and 9 atypical ANCA positive patients. The average age was 55 years (2 to 89). Thirty-three percent of p-ANCA and 24% of c-ANCA positive patients had renal failure (average creatinine of 3.3 mg/dl and 1.9 mg/dl respectively). There were no significant differences in hemoglobin, mean erythrocyte sedimentation rate and leukocytes in the groups. The most frequent complaints were asthenia, anorexia, fever, arthralgia, dyspnea and hematuria. Final diagnosis included granulomatosis with polyangiitis, microscopic polyangiitis, autoimmune hepatitis, ulcerative colitis and Chron´s disease. The most commum iatrogenic complications were linfopenia, infection and diabetes. Six patients died. The average age and creatinine of these patients were higher than those who survived.

Conclusion

ANCA associated vasculitis is a group of rare diseases in our hospital affects both gender and have unspecific clinical manifestations. The ANCA test and renal biopsy were the main diagnostic tests. Older age and higher creatinine were associated with a worse prognosis.

AUTO1-0925
SHORT ORAL DISCUSSION 18 - VASCULITIDES, HORMONES AND AUTOIMMUNITY (STATION 2)

PROFILING THE AUTOANTIBODY REPERTOIRE IN VASCULITIS

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Background

Vasculitis is a chronic autoimmune condition affecting blood vessels that results in organ damage and considerable mortality and morbidity. Currently, our inability to predict which patients will suffer from disease relapses means that long-term immunosuppressive treatments with heavy side effects are the only available therapeutic choices. Within this context, an international effort is ongoing with the ambition to identify candidate biomarkers to personalize vasculitis patients´ treatment. As part of this project, our aim is to profile the reactivity to protein fragments in patients with ANCA-associated vasculitis (AAV), and Large-Vessel Vasculitis Giant Cell Artheritis (GCA), and it's overlapping disease Polymyalgia Rheumatica (PMR).

Method

Screening was performed using planar and bead-based arrays generated using protein fragments from the Human Protein Atlas (www.proteinatlas.org) as antigens. Over two years, more than 500 serum samples collected from AAV and GCA/ PMR patients and healthy controls, were screened for their reactivity towards nearly 2,000 antigens representing 1,520 unique human proteins.

Results

An untargeted screening on planar antigen arrays identified 84 reactive antigens that were selected for further analysis. After complementing this selection with a generous selection of targets mentioned in the context of vasculitis in the literature, the antigens were recoupled to beads to create a 371-plex bead-array representing 240 proteins. Samples from AAV, GCA/PMR, healthy and inflammatory controls were tested. GCA/PMR patients showed high reactivity towards endothelial and smooth-muscle enriched proteins, which is absent or lower in AAV patients and controls.

Conclusion

The identified patterns of reactivity linked to treatment and timepoint will be confirmed with further analysis.

AUTO1-0948
SHORT ORAL DISCUSSION 19 - NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY (STATION 1)

SERUM MATRIX METALLOPROTEINASE-3 NORMALIZATION IS A POTENTIAL PREDICTOR FOR LESS ONE-YEAR RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS

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Background

Our previous study showed continuously elevated serum matrix metalloproteinase (MMP)-3 predict radiographic progression in rheumatoid arthritis (RA) (*Arthritis Res Ther. 2015*). Whether serum MMP-3 normalization is a predictor for better outcome remain elusive. Here we explored the association of serum MMP-3 normalization with clinical and radiographic outcome in RA.

Method

RA patients with moderate to high disease activity (DAS28-CRP>3.2) were followed up at regular intervals. Serum MMP-3 was detected by ELISA at baseline and each visit (1st, 3rd, 6th and 12th months). Hand/wrist X-ray at baseline and 12th month were assessed with the Sharp/van der Heijde modified sharp score (mTSS).

Results

There were 200 RA patients finished one-year follow-up and 58(29%) showed radiographic progression (mTSS≥0.5). RA patients without radiographic progression had significant lower MMP-3 than those with progression at baseline and each visit (Figure 1A, all P<0.001). There were 13.0%, 14.5%, 17.0%, 25.5% and 31.0% patients having normal MMP-3 at baseline and each visit, with significantly lower percentage of these patients showing radiographic progression than those with elevated MMP-3 (Figure 1B, all P<0.05). Among patients with normal CRP at each visit, significantly lower percentage of these patients with normal MMP-3 showed radiographic progression than those with elevated MMP-3 (Figure 1C, all P<0.05). Among patients achieved therapeutic target at each visit, significantly lower percentage of these patients with normal MMP-3 showed

radiographic progression than those with elevated MMP-3 (Figure 1D, all *P*<0.05).

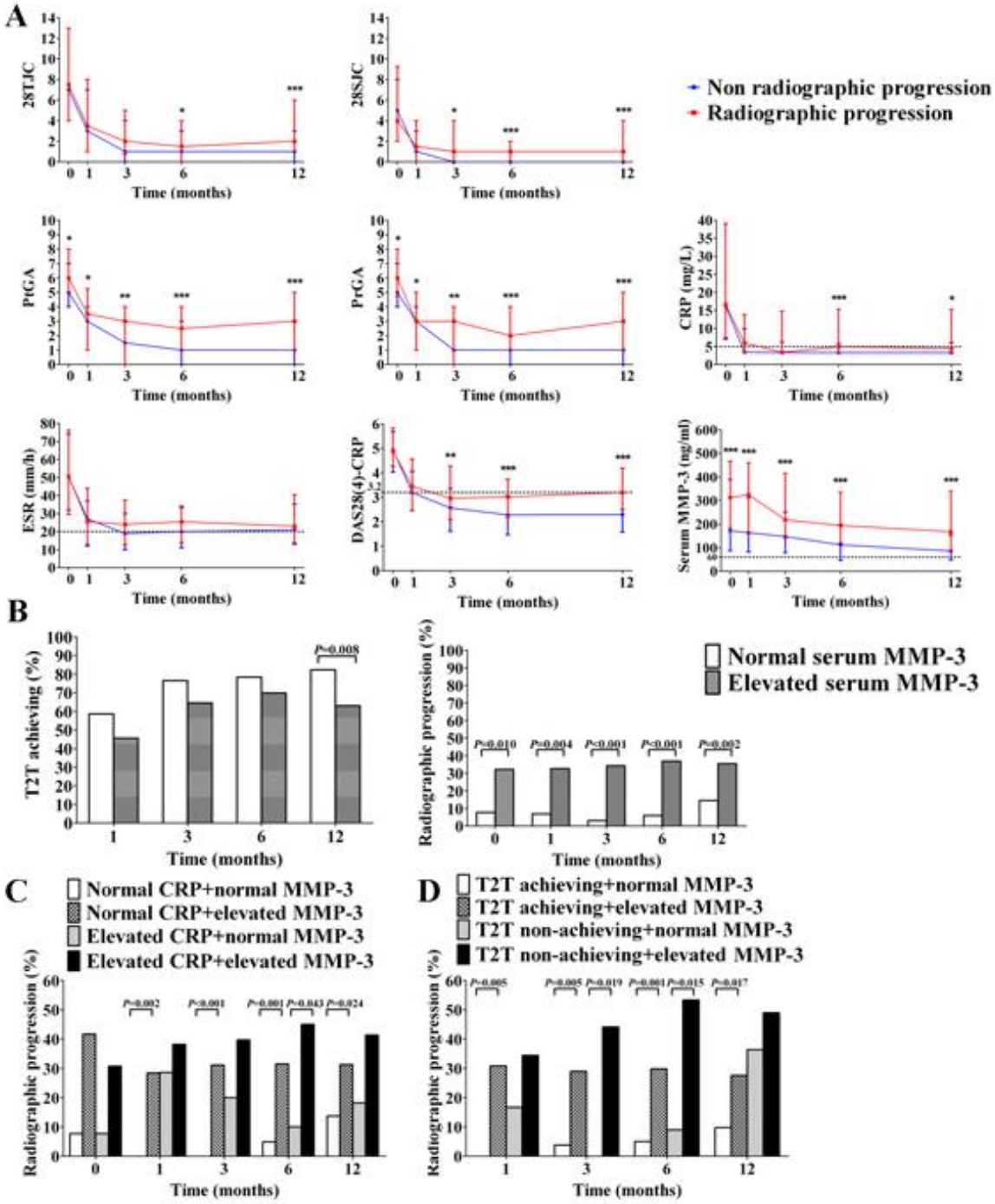

Figure 1 Dynamic change of serum MMP-3 and other indicators in RA patients.
A Comparison of disease activity and radiographic progression indicators between RA patients with and without radiographic progression. **B** Comparison of T2T achieving and the percentage of RA patients showing radiographic progression between normal and elevated serum MMP-3 groups at each visit. **C** Comparison of the percentage of RA patients showing radiographic progression among groups with or without normal CRP and serum MMP-3. **D** Comparison of the percentage of RA patients showing radiographic progression among groups with or without T2T achieving and normal serum MMP-3.

Conclusion

Serum MMP-3 normalization may be a potential predictor for less one-year radiographic progression in RA.

AUTO1-0949
SHORT ORAL DISCUSSION 19 - NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY (STATION 1)

PHARMACOKINETICS AND SAFETY PROFILING OF A SELECTIVE ANTIBODY-SCAVENGING GLYCOPOLYMER, A PROMISING DRUG CANDIDATE FOR THE TREATMENT OF ANTI-MYELIN ASSOCIATED GLYCOPROTEIN NEUROPATHY.

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Background

Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating polyneuropathy that is caused by pathogenic monoclonal IgM antibodies against MAG. These autoantibodies specifically recognize the human natural killer-1 (HNK-1) glycoepitope, which is highly expressed on MAG. Patients suffer from paresthesia, sensory ataxia, tremor and a varying degree of sensorimotor deficits, but no safe and efficacious treatment is available. Therefore, we developed a glycopolymer, PPSGG, which presents a mimetic of the HNK-1 epitope in a multivalent manner on a biodegradable polymer backbone, and demonstrated its therapeutic potential as a selective scavenger for anti-MAG autoantibodies in an immunological mouse model.

Method

In this study, we explored the pharmacokinetic properties of PPSGG and some toxicological parameters by using imaging tools (two-photon tomography, confocal microscopy) and immunoassays (ELISA, Luminex).

Results

Tissue distribution was explored after injection of a fluorescently labeled PPSGG in wild type mice and revealed a predominant presence of the drug in the liver and spleen. The presence of PPSGG in the marginal zone of the spleen, co-localization with the macrophages marker F4/80$^+$ in the liver and the short half-life ($t_{1/2}$, 16.9 ± 5.5 min) of the drug suggest a fast uptake and metabolism by the mononuclear phagocyte system. Additionally, PPSGG did not induce any immunotoxicity or anti-drug antibody formation *in vivo* in mice, and no hepatoxicity in a human liver microtissue model.

Conclusion

In conclusion, all obtained results so far are in favor of the clinical use of PPSGG in selective autoantibody removal.

AUTO1-0018
SHORT ORAL DISCUSSION 19 - NOVEL THERAPEUTIC TARGETS IN AUTOIMMUNITY (STATION 1)

CHANGES IN THE LEVEL OF TGF BETA 1, (CTXII), MYLOPEROXIDASE (MPO) AND SERUM LEPTIN AFTER THREE MONTHS INTAKE OF ALENDRONATE SODIUM IN PATIENTS WITH OSTEOARTHRITIS

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Background

Osteoarthritis(OA) is a common arthritic disorder and responsible for 2 % of disability of people in all world. OA is affects all joint structure including cartilage, bone and synovium which characterized by degradation of cartilage, subchondral bone turn over and osteophytes formation.

The aim was to evaluate the effect of alendronate sodium (ALN) on disease activity and physical function, the biochemical parameters that are related to OA, as well as study the impact of ALN on bone anabolic markers, degradative markers, MPO and leptin, and to determine its effectiveness in slowing progression of disease.

Method

116 OA patients over 45 years old with Kellgren and Lawrence X-ray grade II and more were enrolled. Baseline assessment was done, WOMAC scoring, body mass index and the biochemical parameters with enzyme-linked immunosorbent assay (ELISA) analysis of serum TGF (transforming growth factor) beta 1, C-terminal cross linked -telopeptide of type II collagen (CTXII), Myloperoxidase (MPO) and Leptin). They were instructed to take alendronate sodium (ALN) 10 mg daily for 3 months. Reassessment was done after 3 months.

Results

Significant symptomatic improvement in WOMAC scoring regarding pain, stiffness and function were observed, with significant reduction in serum CTXII, Leptin and TGF beta 1. A non significant reduction in serum calcium, serum Alkaline phosphatase, MPO and joint space width were also reported

Conclusion

Alendronate in osteoarthritis is effective in reducing symptoms especially pain probably through inhibition of leptin and TGF beta 1 with no significant structural improvement, despite reduction of CTXii. ALN was safe in old patients with dyslipidemia.

AUTO1-0999
SHORT ORAL DISCUSSION 2 - EXPERIMENTAL AUTOIMMUNE MODELS (STATION 2)

DISSECTING DISEASE MECHANISMS IN ANTI-GANGLIOSIDE NEUROPATHIES USING AN iPSC-BASED MODEL

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Background

Multifocal Motor Neuropathy (MMN) is a slowly progressive disease characterized by conduction block in motor axons that leads to asymmetric weakness in distal limbs without significant impact on sensory function. The presence of IgM antibodies against the ganglioside GM1 in MMN is a long-established finding, but their role in disease etiology is less understood. This is also true for the IVIg therapeutic mechanism, which lessens complaints and slows disease progression in most patients.

Method

We have developed the first disease model for MMN by adding patient sera to induced pluripotent stem cell-derived spinal motor- and sensory neurons (iPSC-neurons).

Results

IgM-anti-GM1 in MMN patient sera caused both complement-mediated structural damage and complement-independent disruption of calcium homeostasis in iPSC-derived motor neurons. Both effects were prevented by IVIg.

Monoclonal antibodies against the gangliosides GM1, GD1a and GD1b revealed that while both motor and sensory neurons expressed GM1, there were subtle differences in ganglioside epitopes. We are also comparing the expression of the complement-regulating factors CD46, CD55 and CD59.

Patch-clamp experiments revealed differences in electrophysiological characteristics between iPSC-derived motor- and sensory neurons.

Conclusion

The slightly different ganglioside epitopes in iPSC-derived motor- and sensory neurons may result in differential binding of some patient-derived anti-GM1 antibodies, indicating a potential mechanism for motor neuron selectivity in MMN. Expression of complement regulating factors by neurons may also modulate the pathogenic capacity of autoantibodies.

Finally, electrophysiological differences may influence the susceptibility of neurons to conduction block in response to antibody-induced changes in ion channel activity.

AUTO1-1007
SHORT ORAL DISCUSSION 2 - EXPERIMENTAL AUTOIMMUNE MODELS (STATION 2)

MANIPULATION OF THYMIC AND PERIPHERAL TOLERANCE BY AIRE DEFINES DISTINCT TISSUE-SPECIFIC AUTOIMMUNITY

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Background

Tissue-specific autoimmune diseases are assumed to arise from the malfunction of two checkpoints for immune tolerance: defect in the elimination of autoreactive T cells in the thymus, and activation of these T cells by the corresponding autoantigens in periphery. However, evidence for this model featuring the separation between thymic and peripheral tolerance is not sufficient. Furthermore, spectrum of tissue-specific autoimmunity caused by the breakdown of each or combined tolerance mechanism has not been tested.

Method

Using NOD mouse model in which the defect in the thymic and peripheral tolerance coordinately causes type I diabetes, we have investigated these issues.

Results

Transgenic expression of human AIRE in peripheral antigen-presenting cells (APCs) resulted in the resistance to the diabetes due to the defective presentation of b-islet antigens in periphery. In contrast, transgenic human AIRE expression in thymic stroma did not affect the production of diabetogenic T-cells in the thymus. These results were contrasting to our recent demonstration that human AIRE expression both in the thymic and peripheral APCs resulted in the paradoxical development of muscle-specific autoimmunity.

Conclusion

Our results highlighted that thymic, peripheral or combined tolerance mechanism control distinct spectrum of tissue-specific autoimmunity, which can be manipulated by the AIRE/Aire expression in each or both processes.

AUTO1-0811
SHORT ORAL DISCUSSION 2 - EXPERIMENTAL AUTOIMMUNE MODELS (STATION 2)

THE CORRELATION BETWEEN THE NUMERICAL STATUS OF TH22 CELLS AND SERUM LEVEL OF IL-22 WITH SEVERITY OF ULCERATIVE COLITIS

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Background

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease, yet its etiology as well as pathogenesis remains poorly understood. There is increasing evidence that aberrant expression of CD4+T lymphocytes plays an essential role in the progression of different pathologies such as UC. This study aimed to evaluate the circulatory frequency of T-helper 22 (Th22), a subset of CD4+ T cells, and serum level of its signature cytokine, IL-22, in patients with UC.

Method

Blood samples from 30 patients with UC and 30 controls (n=30) were tested for IL-22 level and circulatory Th22-cell count by ELISA and Flow cytometric analysis, respectively.

Results

Our results revealed higher serum level of IL-22 as well as circulatory frequency of Th22 cells in patients with UC compared to those in healthy controls. Notably, effective factors on severity of the disease were age, Th22, IL-22, ESR and CRP.

Conclusion

We conclude that elevated circulating Th22 cells and their signature cytokine, IL-22, may be implicated in the pathogenesis of UC. These findings may provide preliminary experimental clues for the development of new therapies for UC and its severity judgment.

AUTO1-0840
SHORT ORAL DISCUSSION 2 - EXPERIMENTAL AUTOIMMUNE MODELS (STATION 2)

AUTOIMMUNITY AND REPRODUCTION – LESSONS FROM THE ANIMAL MODELS

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Background

SLE is a polygenic autoimmune disorder involving multiple organs that can influence female fertility. Pristane-induced mouse model of SLE is very suitable to study female fertility compared to the healthy animals with the same background.

Method

Lupus-like symptoms were induced through intraperitoneal injection of hydrocarbon oil pristane in non-autoimmune Balb/c mice. Flow cytometry was used for the detection of CD25/CD69 activation markers and apoptosis assay. The levels of cytokines, autoantibodies in the sera and the number of autoantibody-producing plasma cells were quantified by ELISA, ELISpot and protein array.
After hormonal ovarian stimulation, ovulated oocytes were derived from oviducts. Chromatin, tubulin and actin structures were detected by Hoechst 33258, FITC-labeled alpha-tubulin antibody and rhodamine-labeled phalloidin, respectively.

Results

A single i.p. injection of pristane leads to the development of the typical SLE symptoms such as production of different autoantibodies accompanied by massive glomerular depositions of IgG-containing immune complexes in the kidneys, and proteinuria.

The total number of obtained metaphase oocytes from lupus mice was significantly lower compared to healthy controls. The maturation rate, i.e. the proportion of eggs reaching metaphase II, was 9,8% for Lupus mice,12,7% for 7 months old controls and 14,3% for the young controls.

For each oocyte, four characteristics were described – spindle morphology, actin cap, chromosomal condensation and alignment. Many specific abnormalities in the lupus group were found.

Conclusion

Pristane-induced mouse model of lupus exhibited numerous impairments of the reproductive system which may result due to disease activity, autoantibodies or damage in molecular mechanisms through the process of reproduction.

AUTO1-0603
SHORT ORAL DISCUSSION 20 - COMPLEMENT IN AUTOIMMUNITY (STATION 2)

OUTCOME OF PREDISOLONE TREATMENT OF IDIOPATHIC MEMBRANOPROLIFERATIVE

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Background

Outcome of predisolone treatment of idiopathic membranoproliferative

Method

Outcome of predisolone treatment of idiopathic membranoproliferative

Results

Outcome of predisolone treatment of idiopathic membranoproliferative

Conclusion

Outcome of predisolone treatment of idiopathic membranoproliferative

AUTO1-0955
SHORT ORAL DISCUSSION 20 - COMPLEMENT IN AUTOIMMUNITY (STATION 2)

ANTI-C1Q ANTIBODIES AS OCCURRING IN SYSTEMIC LUPUS ERYTHEMATOSUS MIGHT BE INDUCED BY AN EPSTEIN-BARR VIRUS-DERIVED ANTIGENIC SITE

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Background

Previous infection with Epstein-Barr virus (EBV) has been described to trigger autoimmunity and to drive autoantibody generation as occurring in patients with systemic lupus erythematosus (SLE). Independently, complement C1q has also been reported to be involved in the pathogenesis of SLE. Moreover, autoantibodies targeting C1q (anti-C1q) are considered to alter the course of the disease. By studying a major antigenic site of C1q targeted by anti-C1q (A08), we aimed to determine environmental factors and mechanisms leading to the development of anti-C1q.

Method

The cryptic epitope of C1q (A08) was analyzed in a large cohort of SLE patients by protein-based /peptide-based immunoassays, followed by a proof-of-concept study in C1qa-/- mice.

Results

We found that binding of anti-C1q to critical antigenic residues of A08 depends on amino acid-identity. Anti-C1q of SLE patients targeting these critical antigenic residues specifically cross-reacted with the EBV-related EBNA-1-derived peptide EBNA348. In a cohort of 180 SLE patients we confirmed that patients being seropositive for EBV and recognizing the EBNA348 peptide had increased levels of anti-A08 and anti-C1q, respectively. The correlation of anti-EBNA348 with anti-A08 levels was stronger in SLE patients than in matched healthy controls. Finally, EBNA348 peptide-immunization of mice induced the generation of cross-reactive antibodies, which recognized both, the A08 epitope of C1q and intact C1q itself.

Conclusion

These findings suggest that anti-C1q in SLE patients could be induced by an EBV-derived epitope through molecular mimicry, thus further emphasizing the pathogenic role of EBV in the development of SLE.

AUTO1-0679
SHORT ORAL DISCUSSION 20 - COMPLEMENT IN AUTOIMMUNITY (STATION 2)

IS COMPLEMENT (CH50) A MARKER FOR DEPRESSION IN SLE PATIENTS?

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Background

Women are predominantly affected by lupus, which brings significant costs into their personal, family and professional lives. Depressive symptoms, albeit very common, are still not completely understood.Biological mechanisms have been implicated, namely brain inflammation, interaction of auto-antibodies with antigens and cytokine expression triggering neurotransmitter dysfunction. We aimed to identify biological markers associated with the presence of depressive symptoms in women with lupus.

Method

Thirty patients with lupus presenting depressive symptoms were compared with 42 lupus patient's without depression and 13 patients with depression free of autoimmune disease. A battery of instruments was used to assess psychosocial variables, and added to the laboratory and clinical evaluation. Scores for fatigue (CFS & FSS), depression (HADS), anxiety (HADS), overall health (SF-36 & PSQI) and intimate relationship satisfaction (RAS & CSI) were correlated with lupus clinical profiles and laboratory test values.

Results

Similar laboratory data were found between the SLE depressed and non-depressed groups save for the total complement (CH50) levels ($p = 0.032$). Patients with lupus and depression showed a negative correlation between complement (CH50) ($p = 0.032$), and SF-36 and depression. This group of patients also had higher levels of fatigue compared to the depressed control cohort (3.68 ± 1.09) ($p < 0.0001$).

Conclusion

Low complement is a marker of inflammation and disease activity in lupus, and presente results suggest that heightened immune dysfunction and associated disease activity correlates with more depression. The findings highlight the importance laboratory monitoring of immune dysfunction, as possible signs of more discrete symptoms as fatigue, pain, anxiety and depression.

AUTO1-0064
SHORT ORAL DISCUSSION 20 - COMPLEMENT IN AUTOIMMUNITY (STATION 2)

DURING FEVER, WHY OUR BODY ACTS AGAINST FACTS OF PHYSICS?

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Background

During fever, none of medical books describes why our body acts against Facts of Physics .

Method

According to the facts of physics, if temperature increases, thermal expansion of an object is positive it will expand and with decrease of temperature it will shrink. Pressure will increase due to increase of temperature.

On the contrary, during fever we can see blood vessels and skin are shrunk, pressure decreases, body shivers, sleep increases, motion decreases, inflammation increases, body pain increases, blood circulation decreases, dislike cold substances etc...

In fever, the firing rate of Warm sensitive neurons decreases, and the firing rate of

Cold sensitive neurons increases.

At the same time if we apply hotness from outside by thermal bag or if we drink hot water, our body acts according to the Facts of Physics- increase of temperature pressure will also increase, expands blood vessels and skin, body sweats, motion will increase, inflammation will decrease , body pain will decrease, blood circulation will increase, like cold substances etc.

Results

when disease increase, it is the sensible and discreet action of brain that tends to act against facts of physics to sustain life or protect organ .There is no way other than this for a sensible and discreet brain to protect the life or organ.

Conclusion

Fever is a adaptation of the body to increase blood circulation to important organs of the body so our body acts against facts of Physics.

AUTO1-0220
SHORT ORAL DISCUSSION 20 - COMPLEMENT IN AUTOIMMUNITY (STATION 2)

ANTI-IDIOTYPE scFv GENERATED AS STRUCTURAL ANALOGUES OF C1q GLOBULAR AUTOEPITOPES

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Background

The serum protein C1q is an autoantigen in several autoimmune disorders in humans, most notably in systemic lupus erythematosus (SLE). Yet the immunogenic stimulus for the development of anti-C1q autoantibodies is still unknown.

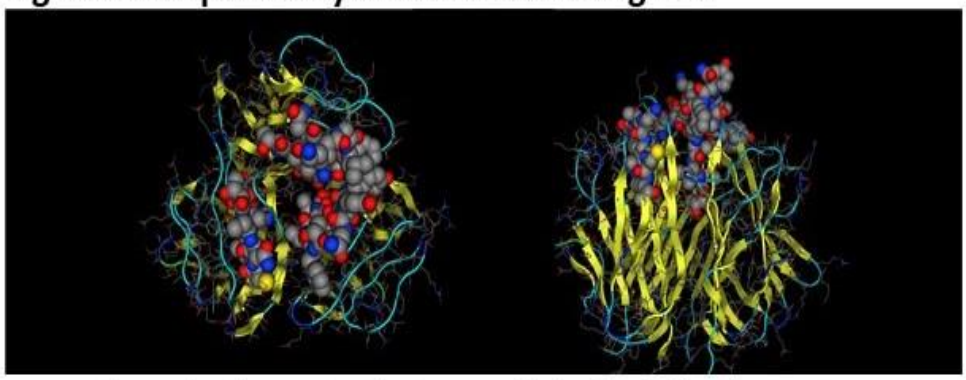
Method

We addressed that issue by studying the structural features of C1q autoepitopes that are recognized by the polyclonal anti-C1q. We used six fractions of anti-C1q with presumed different epitope specificities as antigens for the generation of anti-idiotypic scFv antibodies from the phage library “Griffin1”. The six fractions of anti-C1q were affinity purified from previously characterized Lupus Nephritis (LN) sera.

Results

The monoclonal scFv A1 was found to have approximately 50 % inhibitory capacity on the recognition of C1q by the LN autoantibodies. It was sequenced and *in silico* folded into a 3D structure which was superimposed on the crystalized 3D structure of the globular domain of C1q thus revealing a structural homology with the globular fragments of all three types of polypeptide chains comprising C1q, designated
ghA, ghB and ghC (fig1)

Figure 1. C1q mimicry of scFv A1 CDR regions



Based on the loop similarity model, all of the three CDR regions of scFv V_H have analogs in the apex of native gC1q, which exhibit marked differences in their surface patterns, with respect to both charged and hydrophobic residues.

. The V_H CDR2 of A1 structurally mimicked the ghA sequence GSEAD suggested as a cross-epitope between anti-DNA and anti-C1q antibodies (table1). The scFv A1 was further revealed to inhibit the recognition of ghA by the LN autoantibodies.

Table 1. Loop similarity between scFv A1 and C1q

CDR1	H		G	G	S	F	S	G	Y	Y	
Ac1q		55-60	L	S	Q	W	E	I	C	L	
Bc1q		82-91	D	Y	A	Y	N	T	F	Q	V
Cc1q		79	H	T	S	K	T	N	Q	V	
CDR2	H		I	N	H	S	G	S	T		
Ac1q		121-128	D	A	E	S	G	Q	Y	I	
Bc1q		116-123	G	N	E	G	A	N	S	I	
Cc1q		56-63	A	S	H	T	A	N	L	C	
CDR3	H		A	R	S	H	S	A	A		
Ac1q		81-88	T	T	N	K	G	L	F	Q	
Bc1q		36-43	A	S	S	R	G	N	L	C	
Cc1q		112-119	V	G	I	Q	G	S	D	S	

R,H,K -> positively charged in darker gray; D,E -> negatively charged in dark gray; S,T,N,Q,P,C -> polar uncharged (H-bonds) in gray; G,A,V,I,L,M,F,Y,W -> hydrophobic in light gray.

Conclusion This data suggests that scFv A1 is a structural analogue to a globular autoepitope of C1q and can be further subjected to *in vivo* functional analysis. Other potential inhibitors are the monoclonal scFv F6, F9 and A12.

Acknowledgement. The experimental work was financed by Grant DN01/9 of the Bulgarian NSF.

AUTO1-0913
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

AUTOIMMUNE NEUROLOGICAL DISORDER WITH ANTI-MA2/TA ANTIBODIES IN A PEDIATRIC PATIENT

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Background

Autoimmune neurological diseases remain a complex issue to research. Recent studies led to the discovery of a group of nervous system inflammatory diseases. These diseases develop secondarily to the expression of intracellular anti-onconeural antibodies and of antibodies related to neuronal cell-surface structures. They can present with a variety of clinical symptoms.

Method

The clinical history of the 9 year old girl described in our case report demonstrates the complexity of these disorders. She initially presented to hospital with myoclonus, ataxia and behavioral deterioration a few weeks after recovery from an infection. Opsoclonus-Myoclonus-Ataxia (OMA) syndrome was suspected as an initial diagnosis and immunomodulatory treatment was initated. ANA and anti-Ma2/Ta antibodies were found after diagnostic tests. She presented with four relapses and remissions over the next four years despite treatment. All relapses were additionally characterized by major behavioral changes, namely aggression, irritability and emotional instability. Symptoms of hepatitis of autoimmune etiology appeared during the last relapse.

Results

Since Ma2 antibodies are commonly present in the context of paraneoplastic syndrome, diagnostics directed at tumor recognition were performed.

Conclusion

This disease course shows the necessity of systematic control diagnostics and the uncertainty of prognosis in such patients.

AUTO1-0935
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

UNRAVEL THE TISSUE ROLE IN MULTIPLE AUTOIMMUNITY SYNDROME PATHOGENESIS IN A MOUSE MODEL

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Background

Autoimmunity occurs when lymphocytes recognizing self-antigens escape immune regulatory controls and engage in pathogenic inflammatory responses leading to disease. Many factors are believed to play a role in the development of autoimmunity, and conditions related to the affected tissues are one of them. Our focus is to specifically address whether the ability of the host parenchyma to accommodate with stress and damage influences the development and extent of autoimmune pathology.

Method

We tested different experimental systems to induce imbalanced immune regulation leading to systemic autoimmunity in mice: the DTR and the DEREG mouse models that allow controlled depletion of Treg upon diphteria toxin administration.

Results

We defined the minimal dose and regimen that is innocuous in WT mice and leads to multi-organ targeting in experimental animals. In order to achieve our goal, we explored two different approaches to disentangle the role of cytoprotective mechanisms in parenchymal tissues vs immune cells: total lymph nodes cells transfer and bone marrow chimeras in a Rag KO background. Under controlled regulatory T cell depletion, by the use of a DTR mouse model, we trigger systemic autoimmunity.

Conclusion

We conclude this system is an ideal tool to test variations in disease severity upon loss or gain of function in stress and damage pathways.

AUTO1-0988
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

ACPAs BRIDGE THE DIVIDE BETWEEN INNATE IMMUNITY AND ADAPTIVE IMMUNITY IN RHEUMATOID ARTHRITIS

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Background

Rheumatoid Arthritis (RA) is a prototypical auto immune disease whose occurrence requires the interplay between innate immunity and autoimmunity under predisposing genetic background centered on the production of specific autoantibodies, anti-citrullinated peptides antibodies (ACPAs).The production of anti-citrullinated peptide antibodies (ACPAs) requires the participation of both innate immunity and adaptive immunity.

Method

To elaborate the role of ACPA in mediating innate immunity and adaptive immunity in RA, we carried out a literature review in hopping to provide readers with comprehensive basic knowledge, classic theories of the ACPA immunity as well as the latest breakthroughs in this field.

Results

First, environmental factors activate the innate immune system, leading to the production of citrullinated peptides and local inflammation, which contributes to the breach of self-tolerance. Second, externalized citrullinated proteins or its mimic molecule are presented by APCs to auto-reactive T/B lymphocytes, triggering the differentiation and proliferation of naïve T cells to Th or cytolytic T lymphocyte (CTL) cells and the maturation of plasma cells. Finally, ACPA produced by plasma cells evolves through molecular mimicry and epitope spreading and further activates innate immune cells, collaborates with the complement system and stimulates osteoclasts, thereby perpetuating inflammation.

Conclusion

We described a panorama from ACPA production to manifestation. The elucidation of these sequential events in RA may guide the use of proper medical intervention within the appropriate window of specific developmental phases.

AUTO1-0335
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

HIGH MOBILITY GROUP BOX PROTEIN 1 LEVELS AS A DISEASE MARKER OF SYSTEMIC LUPUS ERYTHEMATOSUS IN SUDANESE PATIENTS

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Background

High Mobility Group Box Protein -1 (HMGB-1) is an Alarmin, which functions as a transcription and DNA regulation factor. When released extracellularly, it acts as a cytokine by promoting inflammation. It has been extensively linked to be involved directly in the pathogenesis of Systemic Lupus Erythematosus (SLE). This study was conducted to identify whether HMGB1 can act as a potential disease marker for SLE and to measure HMGB1 levels in Sudanese SLE patients in relation to their disease activity and characteristics.

Method

This was a cross sectional hospital-based study. SLE patients over 16 years old; attending the Rheumatology Clinic at Omdurman Military Hospital were selected. Eighty patients were interviewed on the basis of a questionnaire. Blood samples were collected and serum was obtained. HMGB1 levels were measured by ELISA.

Results

The study revealed that most of them were females with a percentage of 97.5%. All selected patients' samples had high levels of HMGB1, more than 280 pg/ml. High Mobility Group Box Protein-1 levels correlated positively with disease activity with a P value less than 0.01. Also HMGB1 levels showed significant negative correlation with anti dsDNA antibodies and anti Sm antibodies. However, it showed a direct positive correlation with patients with deranged renal function as well as increasing levels of ESR and CRP with a P values less than 0.01.

Conclusion

This study showed that HMGB1 levels are elevated in Sudanese SLE patients. HMGB1 can act as a potential disease marker of SLE especially to evaluate disease activity and possibly predict renal involvement.

AUTO1-0915
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

CRYOGLOBULINS, FREE LIGHT CHAINS AND RHEUMATOID FACTOR IGG AS PROGNOSTIC TOOLS IN HCV-POSITIVE PATIENTS: A PILOT STUDY.

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Background

Background: The clinical spectrum of Hepatitis C virus (HCV) cryoglobulinemia largely varies from an asymptomatic presentation to severe vasculitis and lymphoma. A recent study in non-HCV patients suggests that even low cryoglobulin levels are responsible for severe renal and neurological complications, leading to high morbidity and mortality.

The aim of this pilot study is therefore to identify a panel of biomarkers, easy to assess, in HCV-positive patients with low amounts of cryoglobulins. The possibility of identifying subpopulations at risk may open scenarios for target treatment strategies for HCV patients which have a good cost/benefit ratio for clinical management.

Method

Methods: Serum samples from 44 untreated patients with chronic HCV infection were examined for cryoglobulins, free light chain (FLC) and rheumatoid factor IgG (RF-IgG). Positive cryoglobulin patterns were divided into type III and microheterogeneous, according to Brouet's cryoglobulin classification.

Results

Results: Differences in the FLC k/λ ratio were significantly different in type III cryoglobulin patients, microheterogeneous cryoglobulin patients and HCV-negative patients ($p<0.01$); while the differences were statistically significant with a p-value <0.01 for the sum of k and λ for type III cryoglobulin patients, for microheterogeneous cryoglobulin patients and for HCV-naïve patients. RF-IgG concentrations between groups were significantly different with a p-value of 0.016.

Conclusion

Conclusion: This pilot study hypothesizes that increased FLC levels and the presence of cryoglobulins are associated with more severe and active disease, especially in terms of mortality and comorbidity; high levels of RF-IgG may present at an early stage of autoimmune disease.

AUTO1-0112
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

A NEW CLASSIFICATION SYSTEM FOR IGG4 AUTOANTIBODIES

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Background

IgG4 autoimmune diseases are characterized by the presence of antigen-specific autoantibodies of IgG4 subclass, and contain well-characterised diseases such as MuSK myasthenia gravis, pemphigus and thrombotic thrombocytopenic purpura. Recently several new diseases were identified, and by now fourteen antigens associated with IgG4 subclass are known. The IgG4 subclass is considered as immunologically inert and functionally monovalent. In the context of IgG4 autoimmunity, pathogenicity of IgG4 is associated with blocking of enzymatic activity or protein-protein interaction of their target antigen. Pathogenicity of IgG4 autoantibodies has not yet been systematically analysed in IgG4 autoimmune diseases.

Method

Analyzing the literature, a modified classification system based on Witebsky's postulates to determine IgG4 pathogenicity in IgG4 autoimmune diseases was established, characteristics and pathogenic mechanisms of IgG4 in these disorders were reviewed and a contribution of other antibody entities to pathophysiology by additional mechanisms was found.

Results

As a result, three classes of IgG4 autoimmune diseases emerged: class I where IgG4 pathogenicity is validated by use of subclass specific autoantibodies in animal models and/or in vitro models of pathogenicity, class II where IgG4 pathogenicity is highly suspected but lack a final validation by use of subclass specific antibodies in *vitro* models of pathogenicity or animal models, and class III with insufficient data or a pathogenic mechanism associated with multivalent antigen binding.

Conclusion

Five IgG4 antibodies were validated as class I, five as class II and four as class III. Antibodies of other IgG subclass or Ig class were present in several diseases, and could contribute additional pathogenic mechanisms.

AUTO1-0650
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

CARBAMYLATED VIMENTIN REPRESENTS A RELEVANT AUTOANTIGEN IN LATIN AMERICAN (CUBAN) RHEUMATOID ARTHRITIS PATIENTS

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Background

Antibodies against post traductional modified antigens are established markers for rheumatoid arthritis (RA). As a new consequence of carbamylation, induction of anti-carbamylated autoantibody was observed in RA patients, sometimes prior to onset of the disease.

The objective was to characterize the reactivity of different isotypes of autoantibodies against carbamylated antigens of vimentin in relation to establish rheumatoid factor, citrullinated antigen (ACPA) and markers of disease activity in a so far largely uncharacterized population of Latin American (Cuban) patients with RA.

Method

Antigenic properties of carbamylated vimentin as well as vimentin peptides were analyzed in 101 patients with RA, 50 disease controls and 51 healthy controls. The diagnostic performance was compared with rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies of second generation (anti-CCP2) and anti-mutated citrullinated vimentin (anti-MCV) antibodies.

Results

Prevalence of anti-MCV IgG (86%), anti-carbamylated vimentin IgG (77%) and anti-carbamylated MCV IgG antibodies (65%) were higher than RF IgM (60%) and anti-CCP2 IgG (52%) in this RA cohort. Furthermore, IgM antibody response against carbMCV and carbVIM was observed in 80% and 90.0% of smokers, respectively. Due to a high sensitivity of the IgM antibody isotype of anti-carbVIM of 85.2%, the combination of ACPA with anti-carbVIM IgM provided the best diagnostic performance so far achieved in a RA cohort of this ethnic origin.

Conclusion

We demonstrate a high prevalence of anti-carbamylated vimentin antibodies and correlation to smoking in Latin American (Cuban) RA patients. Anti-carbVIM IgM represent a useful markerin ACPA negative patients and, in combination with ACPA IgG assays optimize the strategy for autoantibody testing.

AUTO1-0120
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

IgM PENTAMER SHAPES AN IRREGULAR STRUCTURE PROVIDING AN OPEN GROOVE TO ASSOCIATE WITH AIM PROTEIN

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Background

Soluble IgM forms a predominant pentameric complex containing an additional small polypeptide J chain. While the IgM pentamer exerts various immune functions such as complement activation to defend against foreign pathogens, it also behaves as a carrier of apoptosis inhibitor of macrophage (AIM, encoded by cd5l gene), which promotes repair process in different diseases, preserving high AIM levels in serum. Since precise manner for the AIM-IgM pentamer association remains unknown, we studied the issue from the structural viewpoint.

Methods

We analyzed the structure of wild type and variant IgM pentamer in the presence or absence of AIM association using a single particle negative-stain electron microscope.

Results

We found an unexpected irregular structure of IgM pentamer, which is a markedly different view from the textbook pentagon model. Interestingly, we found that the pentameric IgM provides a structural groove specifically fitting to AIM protein. The five monomeric IgM appears covalently assembled through the disulphide bond at a cysteine residue (Cys414) within the Fc-CH3 domain, as the complex formation by a variant IgM-Fc where Cys414 is replaced by serine is structurally unstable, resulting in the development of different oligomeric species, none of which has the specific space for AIM association. Accordingly, AIM does not bind to oligomeric variant IgM-Fc. In the absence of J chain, IgM-Fc forms a symmetric hexagon harbouring no space for AIM, which is consistent with the previous observation that AIM does not bind to J-negative IgM oligomers.

Conclusion

Current discovery of the bona fide shape of IgM pentamer advances our structural understanding of pentameric IgM complex, which may further provide new scopes not only of the quantitative and functional regulation of circulating AIM by IgM pentamer, but also about various immune actions mediated by IgM.

AUTO1-0419
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

GLYCANS AS NOVEL IMMUNOMODULATORS IN SYSTEMIC LUPUS ERYTHEMATOSUS. AN OPPORTUNITY FOR A NEW THERAPEUTIC STRATEGY.

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Background

Systemic Lupus Erythematous (SLE) is one of the most challenging autoimmune diseases as it may be presented as a severe, relapsing and disabling immune-mediated disorder with a negative impact in patients 'quality of life and still remaining incurable. Therefore there is an urgent need in the field to identify the biological basis underlying the global loss of self-tolerance that characterizes SLE, envisioning the development of novel and optimized targeted-specific therapeutic strategies.

Method

This pressing need in the clinics sets the ground to this study, in which we have been demonstrating for the first time in SLE that alterations in the cellular expression of specific sugar chains (glycans) is a new mechanism that tips the balance between homeostasis/self-tolerance and autoimmunity. We have been using a multidisciplinary approach using *ex vivo* renal explants from SLE patients together with mouse models of Lupus disease.

Results

Our results have been demonstrating how glycans regulate both innate and adaptive immune responses in SLE pinpointing this a new targeted-specific mechanism that will stimulate the design of new therapeutic strategies in SLE.

Conclusion

Taken together we have identified a new mechanism in SLE pathogenesis that can be therapeutically targeted.

AUTO1-0812
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

THE ROLE OF INNATE IMMUNE SYSTEM AND DENDRITIC CELLS IN THE PATHOGENESIS OF SPONDYLOARTHRITIS

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Background

Recent data suggests primary involvement of the innate rather adaptive immunity in the pathogenesis of spondyloarthritis (SpA) and move away from the classical arthri- togenic peptide theory of HLA-B27 engagement.

Method

A systematic PubMed search using the keywords “spondyloarthritis”, "ankylosing spondylitis", “dendritic cells”, “innate immunity” was performed and relevant articles extracted. The literature data was critically assessed by the authors and summarized.

Results

Innate immune system activation has been shown to trigger experimental spondyloarthritis. Animal models of SpA and studies on patients’ cells demonstrate impaired activation and function of dendritic cells, manifesting as well by defective formation of immunological synapse, decreased stimulatory capacity of allogeneic CD4+ T cells and preferential stimulation of IL23/IL17 axis. Gut interaction with microbiome is believed to result in the incitement of dendritic cells in SpA with further trafficking of those from gut to joints and spine and emerging inflammation. Cells of innate immune system, such as invariant natural killer T cells and innate lymphoid cells are believed to be closely involved in SpA pathology.

Conclusion

Dysfunction of the innate immune system and dendritic cells may play a central role in the pathogenesis of spondyloarthritis

AUTO1-0433
SHORT ORAL DISCUSSION 3 - MECHANISM AND ETIOLOGY OF AUTOIMMUNE DISEASES (STATION 1)

DEFINING AND ADDRESSING THE PRO-INFLAMMATORY CONTRIBUTIONS OF THE ENVIRONMENT VIA CLINICAL ACRONYM AND EVIDENCE-BASED PROTOCOL: HISTORY, PRACTICAL IMPLEMENTATION, & EXEMPLARY CASE REPORTS IN AUTOIMMUNE DISEASE

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Background

Medical/pathology textbooks describe inflammatory diseases as resulting from “genetic predisposition with environmental triggers”; this leaves clinicians disempowered unless the major environmental triggers are defined and translated into practical clinical actions. Thanks to the accumulation of research by thousands of investigators, inflammatory diseases are no longer seen as “idiopathic” but rather now as “multifactorial.” Clinicians must now appreciate each of the major environmental factors that contributes to sustained inflammation and the resulting inflammatory/autoimmune diseases.

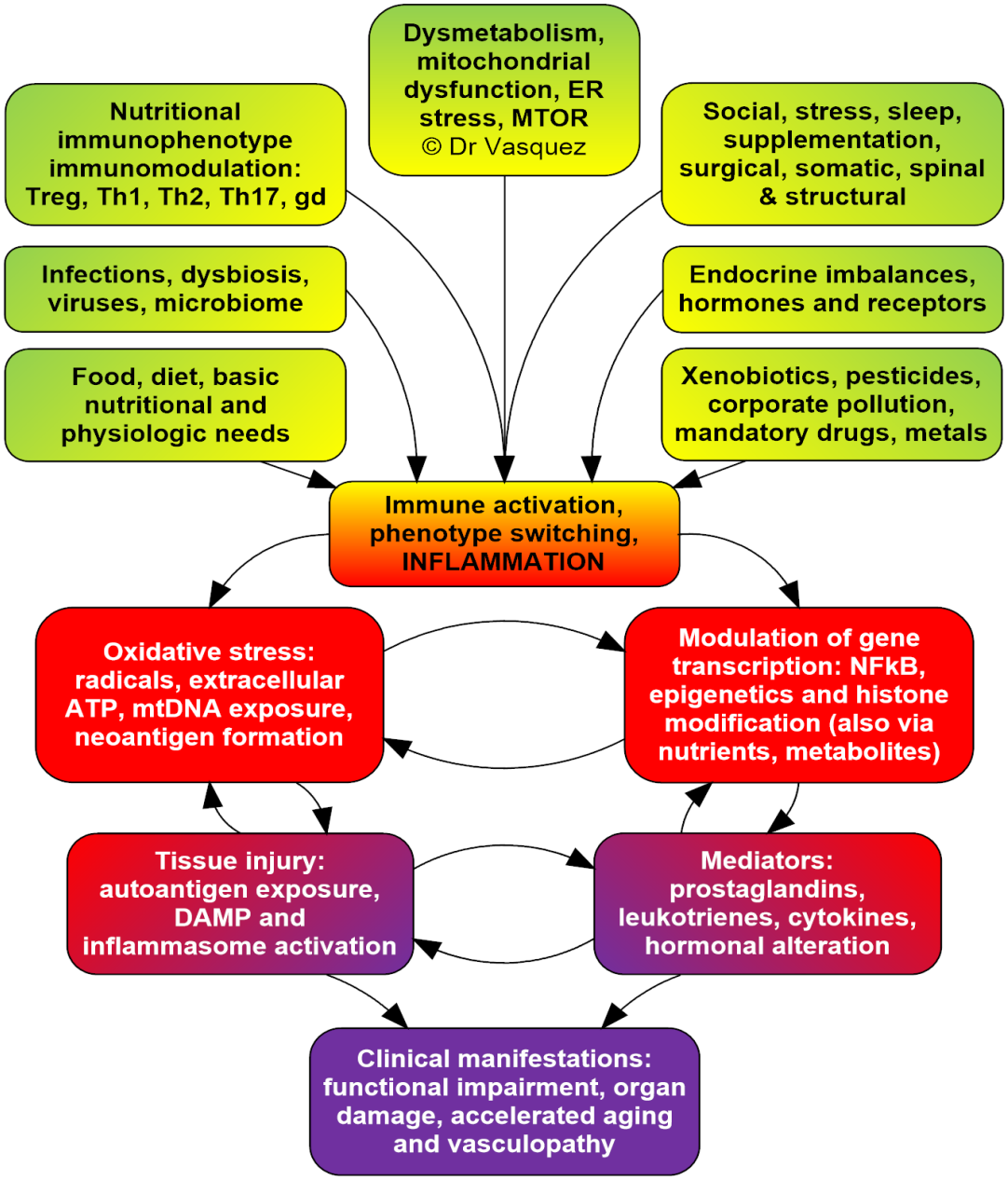
Method

In this presentation, Dr Vasquez defines and organizes the major environmental triggers of inflammatory/autoimmune diseases into an easy-to-remember acronym; clinicians will learn how to assess and address each component of this clinical diagnostic and therapeutic approach. Objective and clinically-reliable biomarkers will be emphasized; treatments discussed will be rigorously evidence-based.

Results

Following review of thousands of articles and work with thousands of patients, the dominant patterns of environmental influences converges into the following categories: Food, Infections, Nutritional modulation of immune and inflammatory (im)balance, Dysmetabolism including dysfunctional mitochondria and MTOR activation, Stress and psychological factors, Endocrine imbalances, and Xenobiotic exposure, including

pollution, pesticides, metals, and forced drugs.



Conclusion

The resulting protocol can be customized per patient, disease, comorbidities, and drug-interactions. For example, the diet is addressed with a 5-part protocol, infections and dysbiosis are investigated by serologic and site-specific microbiologic tests, mitochondrial dysfunction is treated with therapeutic autophagy and biogenesis, lifestyle is assessed and optimized, hormones are assessed serologically and balanced pharmacologically, xenobiotic load is assessed via urine and blood testing followed by depuration, support of cytochrome p450 and substrate conjugation.

AUTO1-0278
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

THE CLINICAL AND DIAGNOSTIC VALUE OF IGA-ANTIBODIES AGAINST CD74 IN AXIAL SPONDYLOARTHRITIS

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Background

Current diagnosis of axial spondyloarthritis (axSpA) is currently based on clinical presentation of a disease and detection of HLA-B27 is not disease specific. Recently, a new biomarker associated with axSpA has been found namely autoantibodies against CD74 *(Baerlecken N.T. et al., 2014).*The purpose of our research was to assess the clinical and diagnostic relevance of IgA autoantibodies against CD74 in patients with axSpA in Russia.

Method

We measured the IgA- antibodies against CD74 in the sera of 68 patients with ankylosing spondylitis (AS), 46 – with nonradigraphic axial spondyloarthritis (nr-axSpA), 26 – with psoriatic arthritis (PsA) and 37 healthy controls by means of quantitative ELISA method (AESKU®, Germany). Statistical analysis was performed using the Fisher's and Mann-Whitney tests.

Results

In patients with axSpA the mean concentration of IgA against CD74 was 3.5±3.0 U/ml, in patients with nr-axSpA – 3.8±2.9 U/ml, whereas in patients with PsA and controls – 2.1±1.4 U/ml and 1.3±1.4 U/ml, respectively (Fig. 1). Cut-off value of autoantibody > 2.0 U/ml in patients with axSpA showed the diagnostic sensitivity of 64.4%, specificity of 89.2%, in patients with nr-axSpA – 73.1% and 84%, respectively (p<0,0001), whereas in patients with PsA – 96.1% and 45.9%, respectively (Fig. 2).

Figure 1. Concentration of IgA against CD74 in the pathients with ankylosing spondylitis, nonradigraphic axial spondyloarthritis and psoriatic arthritis in comparison with the control, * p <0.05

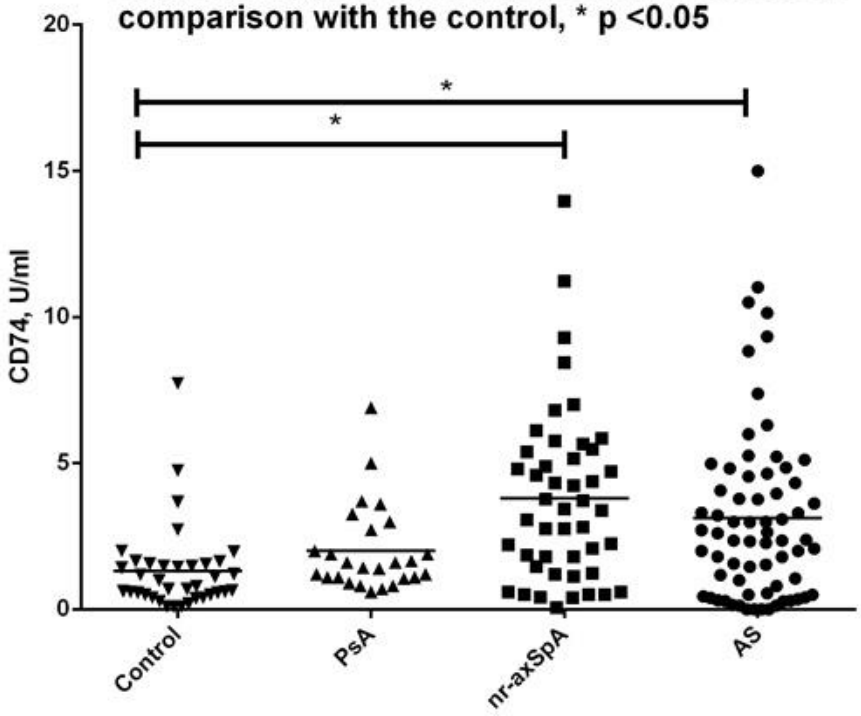
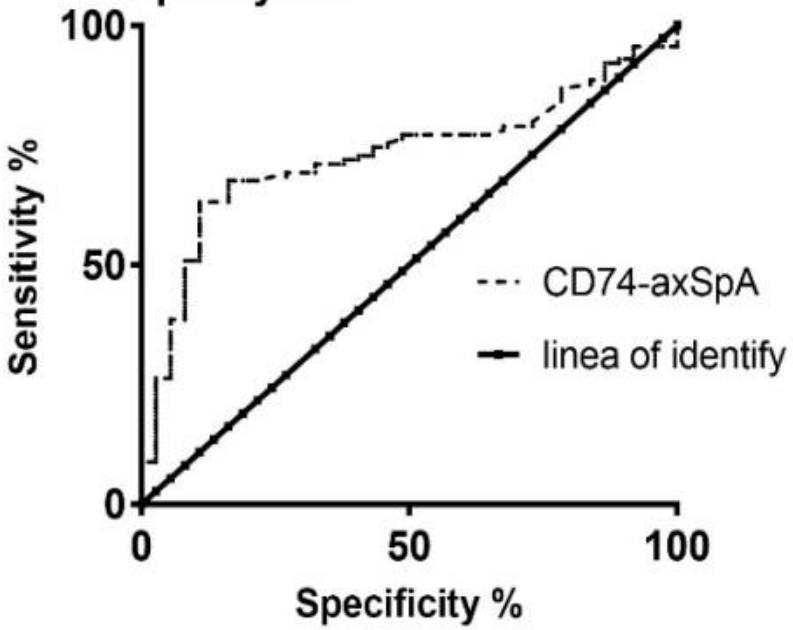


Figure 2. ROC curve of the concentration IgA against CD74 in pathients with axial spondylitis



Conclusion

Autoantibodies IgA against CD74 are potential biomarker for diagnosis axSpA and in differential diagnosis between axSpA and PsA.

AUTO1-0785
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

DETECTION OF ANA PATTERNS INCLUDING DFS70 USING A NOVEL DFS70 KNOCKOUT HEP-2 AND CONVENTIONAL HEP-2 SUBSTRATES: A COMPARATIVE STUDY

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Background

Accurate interpretation of DFS70 pattern can be challenging using conventional HEp-2. Here, we evaluate a novel HEp-2 substrate composed of PSIP1/LEDGF/DFS70knockout cells and its relative performance against conventional HEp-2 in routine ANA screening.

Method

Two thousand three hundred and fifty-six consecutive sera from patients presenting to rheumatology clinic at Xiamen, China were simultaneously screened at 1:100 using a conventional HEp-2 (Euroimmun AG, Lübeck, Germany) and a novel HEp-2 ELITE/DFS70-KO (Trinity Biotech, Buffalo, NY). Serological pattern specificities were confirmed using immunoblot (Euroimmun AG, Lübeck, Germany). The relative performance of two HEp-2 IIF substrates was assessed in the light of the available clinical diagnosis and serological data.

Results

A total of 414 (17.6%) cases were identified as positive for ANAs either by conventional HEp-2 (384, 16.3%) or HEp-2 ELITE (387, 16.4%). Of the 414 positive cases, 357 (86.2%) were positive on both HEp-2, 27 (6.5%) only on conventional HEp-2 and 30 (7.2%) only on HEp-2 ELITE. 53 (92.9%) out of 57 cases that were only positive on one type of substrate reported +/weak positive staining. Of the 414 positive cases, 316 (76.3%) were determined to have identical ANA pattern, 98 (23.7%) differed in pattern which included 57 cases that were negative on one substrate. All nineteen cases identified as DFS70 using HEp-2 ELITE were interpreted as either negative or speckled on conventional HEp-2.

Conclusion

HEp-2 ELITE/DFS70-KO substrate demonstrated comparable performance to conventional HEp-2 in routine ANA screening for patterns excluding DFS70. Nineteen DFS70 cases were reported using the novel HEp-2 were misinterpreted using conventional HEp-2.

AUTO1-0828
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

NEAR PATIENT DETECTION OF ANTI-MDA5 ANTIBODIES USING PHOTONIC RING IMMUNOASSAYS

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Background

The presence of anti-MDA5 antibody is associated with amyopathic dermatomyositis and/or rapidly progressive interstitial lung disease that can be fatal. In the latter case, it is mandatory to confirm the diagnosis as soon as possible in order to initiate aggressive treatments and the presence of anti-MDA5 autoantibodies is an important part of the differential diagnosis.The immunoassay using photonic microrings is a new sensitive technology that enables rapid results in less than 15 minutes. The aim of our study was to evaluate this technology for the detection of anti-MDA5 antibodies in sera with known positivity.

Method

The system is based on immobilizing the antigenic target, MDA5, above the photonic rings in a silicon chip. We analyzed a total of 72 sera drawn from 40 patients known to be positive for anti-MDA5 antibody in our laboratory using immunoblotting assays and 4 negative controls. For some patients, several samples drawn during the follow-up could be analyzed.

Results

Using the photonic ring immunoassay, we could confirm the presence of anti-MDA5 antibody in all samples known as positive for anti-MDA5 antibody by other techniques. No false positive or false negative results were found. Moreover, high levels of MDA-5 antibodies measured at diagnosis are associated withinterstitial lung disease with respiratory functional impairment at presentation. Interstingly, we observed a decrease in anti-MDA5 antibodies titers in followed-up patients.

Conclusion

The photonic ring immunoassay is a fast and reliable technology for the detection of anti-MDA5 antibodies.

AUTO1-0908
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

A NOVEL MURINE MONOCLONAL TSH RECEPTOR-BINDING ANTIBODY ENABLES TSH-RECEPTOR ANTIBODY (TRAB) ANALYSIS

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Background

The serological hallmark of Grave's disease (GD) is the TSH-receptor (TSHR)-autoantibody (TRAb). New assay generations employ monoclonal antibodies (moAbs) for solid-phase TSHR immobilization and as TSH-inhibitors for second ($TRAb^{2nd}$) and third-generation TRAb ($TRAb^{3rd}$) assays, respectively. A novel $TRAb^{3rd}$ ELISA was developed using murine mAb T7 recognizing the TSH-binding site of human TSHR (T7-$TRAb^{3rd}$ assay). Obtained TRAb-levels were compared with $TRAb^{2nd}$ (bovine TSH/porcine TSHR) and $TRAb^{3rd}$ assays (porcine TSHR/human moAb M22 [M22-TRAb $assay^{3rd}$]).

Method

TRAb was determined in 89 patients with GD, 56 with Hashimoto's thyroiditis (HT), 73 with non-autoimmune thyroid diseases (NAITD), 17 with rheumatoid arthritis, and 50 healthy individuals by T7-$TRAb^{3rd}$ (Medizym T.R.A.human, cut-off:1.5 IU/L), M22-$TRAb^{3rd}$ (Medizym TRAbclone, cut-off:0.4 IU/L) and $TRAb^{2nd}$ ELISAs (Medizym T.R.A., cut-off:1.5 IU/L).

Results

According to McNemar's test, there were significant differences between all three TRAb tests using the recommended cut-offs ($p<=0.0005$, respectively). This was due to significantly higher positivities of M22-TRAb $assay^{3rd}$ in HT patients (28/56 vs. 5/51 [$TRAb^{2nd}$] and 11/45 [T7-$TRAb^{3rd}$]) as well as NAITD patients (35/73 vs. 0/73 [$TRAb^{2nd}$] and 4/73 [T7-$TRAb^{3rd}$]); $p<0.002$, respectively. Sensitivity/Specificity obtained by receiver-operating-characteristics-curve analysis (Fig. 1) with optimized cut-offs (1.4, 0.9, 2.0 IU/mL) were 91.0%/96.9%, 91.0%/93.4% and 92.1%/95.4% for $TRAb^{2nd}$, M22-$TRAb^{3rd}$, and T7-$TRAb^{3rd}$ respectively. The use of optimized cut-offs resulted in non-significant differences between all three assays.

Conclusion

Human and murine mAbs recognizing the TSH-binding site of the TSHR may be used for the sensitive and specific detection of TRAb in ELISA. After adjusting cut-offs, both $TRAb^{3rd}$ ELISAs demonstrated similar assay performances and were not significantly different from $TRAb^{2nd}$ ELISA.

AUTO1-1010
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

ANTINUCLEAR ANTIBODY ASSAY RESULT INTERPRETATION IN THE PRESENCE OF HEAVY PROTEINURIA IN PATIENTS WITH RENAL DISEASES

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Background

Majority renal diseases is a manifestation of dysregulated immune system. Both primary as well as secondary autoimmune diseases may affect renal functions resulting in significant proteinuria. Immunological workup of autoimmune diseases begins with testing for the presence of antinuclear antibodies(ANA). ANA in low titer are present nonspecifically in 5%-10% healthy persons, however high ANA titer (≥1:160) is mostly associated with rheumatic disorders. ANA positive results along with relevant clinical information dictates identification of either anti-double stranded deoxyribonucleic acid (anti-dsDNA) or anti-extractable nuclear antigens (anti-ENA) antibodies for the definite diagnosis. Renal diseases which result in heavy proteinuria can affect ANA assay.This study assessed influence of heavy proteinuria on autoantibodies in patients with renal diseases.

Method

150 patients with renal pathology were registered who had positive ANA test. Their serum samples were tested for anti-dsDNA and anti-ENA antibodies. ANA titer of 1:160 was taken as significant. Proteinuria was assessed by spot protein/creatinine ratio. A ratio of ≥1(equivalent to 1 gm protein/day) was considered as heavy proteinuria . Data was analyzed using SPSS software version. 20

Results

Heavy proteinuria was present in 119(79%) patients. Low ANA titer(≤1:80) were present in 37(25%) patients. 33 patients had heavy proteinuria along with low ANA titer. Out of them ANA was characterized in 11 patients. There was no significant difference in the prevalence of various autoantibodies in patients with high or low ANA titer with heavy proteinuria.

Conclusion

Low ANA titer is equally significant in the setting of heavy proteinuria. ANA results should be clinically correlated for adequate patient management

AUTO1-0990
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

NEW AUTOANTIBODIES IN SPONDYLOARTHRITIS

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Background

Spondyloarthritis (SpA) is a common inflammatory disorder. The diagnosis of SpA is often difficult because the lack of specific laboratory biomarker. Clinical examination and x-ray of the spine which show characteristic spinal changes and sacroiliitis are the major diagnostic tools. However, abnormalities in x-ray often occur several years after the onset of the disease. Autoantibodies are widely used as biomarkers in many types of autoimmune diseases and other diseases.

Method

We used proteomic approach to screen new autoantigens in SpA patients.

Results

We detected one new autoantigen in SpA sera named as SPA1. Using ELISA technology, IgG autoantibody to SPA1 was found in 24.4% of the SpA patients. In the controls, the prevalence of the new autoantibody was 6.8% in health controls, 16.7% in systemic lupus erythematosus, 0% in psoriatic arthritis and gout. The titer of anti-SPA1 was close associated with disease activity of SpA.

Conclusion

Antibody against SPA1 could provide an important additional tool for diagnosis of SpA.

AUTO1-0628
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

STROKE IN AUTOIMMUNE DISEASES: PATHOPHYSIOLOGY OF CEREBRAL VESSELS IN RHEUMATOID ARTHRITIS

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Background

The prevalence of strokeis increased in rheumatoid arthritis (RA). Preclinical assessment of intracranial vessels includes transcranial doppler (TCD). TCD performance requires intact temporal acoustic windows (TAW). We assessed RA patients and healthy controls by transcranial Doppler (TCD), carotid ultrasonography and brain MRI.

Method

TAWF and temporal bone were assessed by ultrasound and CT. Several bone biomarkers were assessed by ELISA. Altogether 63 female RA patients and 60 age-matched controls underwent TCD assessment of the medium cerebral (MCA), basilar and vertebral arteries. Pulsatility (PI), resistance (RI) indices and circulatory reserve capacity (CRC) were determined. The presence of carotid plaques and intima-media thickness (cIMT) were also determined. Intracerebral vascular lesions were investigated by brain MRI.

Results

In RA, the right and left TAW were undetectable in 35% and 53% of patients, respectively. MCA PI and RI values increased in the total RA population vs controls. MCA PI(r) and RI(r) is also lower in biologic-treated patients. MCA CRC was also impaired and basilar artery PI was higher in RA. More RA patients had carotid plaques and had increased cIMT. Disease duration, disease activity and anti-CCP may influence left MCA PI and RI, as well as CRC.

Conclusion

TAWF, thicker and heterogeneous temporal bones were associated with RA. This may be the first study to show increased distal MCA and basilar artery occlusion in RA as determined by TCD. RA patients also exert CRC defect. We also confirmed increased carotid plaque formation, increased cIMT. Biologics may beneficially influence some parameters in the intracranial vessels.

AUTO1-0781
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

IS THERE A NEED TO RELOOK AT THE CUTOFFS OF RHEUMATOID FACTOR FOR DIAGNOSIS OF RHEUMATOID ARTHRITIS IN INDIAN POPULATION ?

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Background

Population specific cut offs of titers of Rheumatoid Factor (RF) in diagnosis of Rheumatoid arthritis (RA) and the role of anti citrullinated peptide antibiodies (ACPA) remains unknown.

Method

RF titers of consecutive adult RA patients fulfilling ACR 1987 as well as ACR/EULAR 2010 criteria were compared with healthy normal and diseased non RA controls using ROC-AUC analysis. Reclassification of disease phenotype as seropositive and seronegative RA using various cutoffs was looked into and corresponding Anti-CCP titers analyzed

Results

Overall 589 cases of RA (range: 18-69 years; 29.9% Females) were compared with age and sex matched 192 non RA rheumatology patients and 51 controls. Mean (+-SE) RF titers in RA, healthy controls and non RA patients were107.7 IU/L (+- 6.17), 14.7 IU/L(0.43) and 29.3 IU/L (+- 6.08) respectively. ROC analysis revealed a cutoff titer of 20.3 IU/L (AUC 0.705 (95% CI:0.66-0.74)) with the best combination of sensitivity and specificity. With the cut offs of 60, 40 and 20 IU/L, seropositivity in 286/589 (48.5%), 322(54.7%) and 396 (67.2%) cases respectively. Simultaneous Anti-CCP was done in 480(81.4%) cases: 363 (75.6%) of these were positive.

Conclusion

For this cohort of Indian population, a cut off of 20 IU/L of RF titers has the best performance for a diagnosis of RA with an additional 18.7 % cases labeled as seropositive as against the currently used cutoffs. There is a need to reevaluate the population specific RF titers in conjunction with anti- CCP in Indian population.

AUTO1-0940
SHORT ORAL DISCUSSION 4 - DIAGNOSTIC MEASUREMENTS IN AUTOIMMUNITY (STATION 2)

IS ANTI-DSF70 POSITIVITY REALLY AN EXCLUSION BIOMARKER FOR ANA-ASSOCIATED AUTOIMMUNE RHEUMATIC DISEASES?

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Background

The use of antinuclear antibodies (ANA) detection with an indirect immunofluorescent (IIF) test is considered the mainstay for the screening for ANA-associated autoimmune rheumatic diseases (AARD). The visualization of a dense fine speckled pattern 70 with anti-DSF 70 antibodies) has been considered a biomarker to exclude the diagnosis of AARD.

Method

The authors present a retrospective descriptive analysis within a two-year period (2015-2016) of ambulatory patients who were screened positively on ANA IIF test with a dense fine speckled pattern (589patients) and in whom anti-DSF-70 antibodies were identified using the immunoblot method.

Results

The anti-DSF70 antibodies frequency was determined in 10%.

The median age was of 35,1years, mainly of the female gender (93%). The first analytical request was ordered mostly by internal medicine and pediatry doctors and the main cause of was due to skin (22%) followed by articular disturbances(21%).

The ANA titulation of 1:640 was detected more frequently (82%) comparing to 1:320 (17%). In 7 patients (11,2%), another specific antibody was identified (3 patients with anti-dsDNA, 3 with antiphospholipid and 1 with anti-CCP antibodies) and 1 patient had a positive HLA-B27 result.

An AARD was diagnosed in 18 patients (29%) with SLE being the most frequent disease(8%). The remaining AARD were uniformly less frequent but nonetheless present.

Conclusion

The frequency of AARD was strikingly high (29%) when in comparison to previous studies showing how an AARD can by diagnosed despite the positivity of the ANA-DSF70 determination.

There is negative association between anti-DFS70 antibodies and AARD, but only when no concomitant AARD-specific autoantibodies are found.

AUTO1-0073
SHORT ORAL DISCUSSION 5 - ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE (STATION 1)

ANTI-β2-GLYCOPROTEINMARKER FOR STROKES IN PATIENTS WITH ANTI-PHOSPHO I AUTOANTIBODY EXPRESSION AS A POTENTIAL BIOLIPID SYNDROME

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Background

Anti-phospholipid syndrome (APS) is an autoimmune disease. Cerebral ischemia associated with APS occurs at a younger age than typical atherothrombotic cerebrovascular disease, is often recurrent, and is associated with high positive IgG anti-phospholipid (GPL) unit levels.
This study sought to determine the frequency rates of anti-cardiolipin (aCL) dependent on the presence of β_2-GPI, anti-β_2-glycoprotein I (aβ_2-GPI), and anti-phosphatidyl serine (aPS) IgG autoantibodies among stroke patients, and thus demonstrate the importance of testing for aβ_2-GPI autoantibodies.

Method

For these study, stroke patients and control subjects recruited from Kurdistan / Northeren Iraq were evaluated. All cases were under 50 years-of-age and had no recognizable risk factors**.** Using ELISA to evaluate the presence of IgG isotype of aCL, aβ_2-GPI, and aPS autoantibodies in their blood

Results

the results indicated that the frequency of aβ_2-GPI was 14/50 (28%), aCL was 11/50 (22%), and aPS was 9/50 (18%) among stroke patients. In contrast, aCL was detected in 2/30 (6.7%) of control subjects; each of the other anti-phospholipid antibodies (APLA) was never observed. Of all the aβ_2-GPI$^+$ cases, the incidence of stroke patients having the combined profile of aβ_2-GPI + aCL was 11/14 (78.6%) and of aβ_2-GPI + aPS was 9/14 (64.3%). Only 2/14 (14.3%) of these aβ_2-GPI$^+$ patients also expressed aCL in the absence of aPS.

Conclusion

It can be concluded from these studies that the among the three major forms of APLA examined, the presence of IgG aβ_2-GPI autoantibodies appeared to correlate best with stroke in patients who were concurrently suffering APS.

AUTO1-0850
SHORT ORAL DISCUSSION 5 - ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE (STATION 1)

PROTEOLYSIS-RESISTANT DOMAINS IN β2-GLYCOPROTEIN I (β2GPI): Features And Potent Applications In Lipidomics

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β2-Glycoprotein-I (β2GPI), as a major autoantigen related to antiphospholipid syndrome, is a highly-glycosylated plasma protein composed of five homologous domains which regulates coagulation, fibrinolysis, and/or angiogenesis. Through N-terminal amino acid sequencing, a novel plasmin-cleaved site was identified in its domain V (DV). We further modified the intact DV by altering two amino acids at specific proteolytic cleavage sites to generate three stable DV mutants. SDS-PAGE and MALDI-TOF-MS analysis showed that all three DV mutants were more stable than the intact DV and resistant to proteolysis. The affinities of intact β2GPI and its associated mutants to cardiolipin (CL) were also assessed through competitive ELISA. All DI and DV mutants potently inhibited HUVEC's proliferation and several mutants significantly inhibited HUVEC's tube formation. Moreover, one particular DV mutant-based affinity column has demonstrated its phospholipid-binding capacities towards anionic lipid, acting as a potential lipid purification model. The model could substantially isolate the anionic DOPS from zwitterionic DOPC. In summary, the proteolysis-resistant and unhindered lipid-binding properties of DV mutant has made it an appealing element for subsequent prospective studies. Future in-depth characterizations and optimized applications is expected to complement full capacities of its comprehensive usage, particularly in lipidomics study.

AUTO1-0007
SHORT ORAL DISCUSSION 5 - ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE (STATION 1)

INCIDENCE OF THROMBOEMBOLIC EVENTS IN ASYMPTOMATIC SUBJECTS WITH ANTIPHOSPHOLIPID AUTOANTIBODIES

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Background

The antiphospholipid syndrome (APS) is defined by simultaneous presence of vascular clinical events and antiphospholipid antibodies (aPL). The aPL considered as diagnostics are lupus anticoagulant and antibodies anticardiolipin (aCL) and anti-ß2 glycoprotein-I (aB2GP1). Over the past few years, IgA-aB2GP1 have been associated with thrombotic events both inpatients positive, and mainly negative for other aPL, however its value as pro- thrombotic risk-factor in asymptomatic patients has not been well defined.The objective of the study was to test the role of IgA anti B2GP1 as a risk factor for the development of APS-events (thrombosis or pregnancy morbidity) in asymptomatic population through a follow-up for 5 years.

Method

248 patients isolated positive for anti-beta2-glycoprotein I IgA (Group-1 study) and 228 negative patients (Group-2 control) were studied. All the patients were negative for IgG and IgM aCL.

Results

During the follow-up, 45 patients (9.5%) had APS-events, 38 positive for IgA-aB2GP1 and 7 negative (15.3% vs 3.1%, $p<0.001$). The incidence rate of APS-events was 3.1% per year in IgA-aB2GP1 positive patients and 0.62% per year in the control group. Arterial thrombosis were the most frequent APS-event (N=25, 55%) and were mainly observed in Group-1 patients (21 vs 4, $p=0.001$). Multivariate analysis shown as independent risk-factor for the development of APS-events, age, sex (men) and presence of IgA- aB2GP1 (odds ratio 5.25, 95% CI 2.23 to 12.36).

Conclusion

The presence of IgA-aB2GP1 in people with no history of APS- events is the main independent risk factor for the development of this type ofevents, mainly arterial thrombosis.

AUTO1-0981
SHORT ORAL DISCUSSION 5 - ANTIPHOSPHOLIPID SYNDROME TOWARDS THE THIRD DECADE (STATION 1)

ANTIPHOSPHOLIPID SYNDROME: APPLICATION AND RELEVANCE OF "NON-CRITERIA" CLINICAL MANIFESTATIONS

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Background

Antiphospholipid syndrome (APS) is a thrombotic disorder associated with presence of antiphospholipid antibodies (APA). The "non-criteria" clinical manifestations (NCCM), which are superficial vein thrombosis, thrombocytopenia, renal microangiopathy, heart valve disease (HVD), livedo reticularis, migraine, chorea, seizures and myelitis, are presently being considered as classification criteria.
The objectives of the study are to characterize a sample of APS patients and determine the relevance of the NCCM in persistently positive antiphospholipid antibodies patients (PPAPA).

Method

A retrospective cohort study of 40 patients with APS and PPAPA followed in an outpatient setting of a Portuguese central hospital was performed. The study evaluated gender, current and diagnosis age, duration of illness, concurrent autoimmune disease, affected circulation, type and number of thrombotic events, presence of APA, treatment and NCCM.

Results

Table I characterizes study population. Affected circulation was venous (45.2%), arterial (38.7%) and obstetric (16.1%). Main thrombotic events are deep vein thrombosis (38.7%) and stroke (29%). The majority of patients experienced one event (73.3%). Related to APS, Lupus anticoagulant (LA) and Anticardiolipin antibodies (aCL) are present in 60% and Anti-β-2glycoprotein-I antibody (antiβ2GPI) in 43.3%. In PPAPA, LA occurs in 80%, aCL in 60% and antiβ2GPI in 20%. A total of 67.5% of patients are anticoagulated, of which 11.1% are PPAPA. The NCCM are present in 80% of PPAPA, the most common are migraine (40%), thrombocytopenia (30%) and HVD (20%).

Conclusion

This data reflect existing literature. Patients who do not meet the criteria, mainly PPAPA, should have regular follow-up. Anticoagulation criteria should be reviewed because effective treatment changes disease course.

AUTO1-0499
SHORT ORAL DISCUSSION 6 - PREDICTION, MONITORING AND PREVENTION, PRECISION (PERSONALIZED) MEDICINE IN AUTOIMMUNITY (STATION 2)

LONGITUDINAL PROFILING OF AUTOANTIBODY REPERTOIRES IN 99 HEALTHY INDIVIDUALS

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Background

In the era of personalised and precision medicine, initiatives to profile healthy individuals is rising. One such initiative is the Swedish Scapis SciLifeLab Wellness profiling study (S^3 wellness), which currently is the most extensive study ever performed on healthy individuals.

Method

A set of 101 healthy volunteers, 50-65 years of age, were enrolled and characterised using clinical phenotyping, questionnaires and imaging by MRI, CT-scans and ultrasound analysis. Of these volunteers, 99 persons completed full participation with four visits spanning one year in total time, with health controls, sampling of blood, urine and faeces as well as lifestyle questionnaires and activity monitoring. These samples have been deeply and broadly profiled by a wide range of high-end molecular technology platforms present at SciLifeLab, a Swedish national center for molecular life science research, with the long term aim to support healthy ageing.

Results

Here, we present the autoantibody repertoire of these healthy individuals, profiled as the IgG reactivity towards an antigen array comprising 360 pre-selected antigens. We show that autoantibody reactivity profiles resembles unique barcodes for each individual and are maintained over time. The reactivity profile is personal in regards of baseline signal, the number of reactivity peaks and towards which antigens one individual shows reactivity. On this set of 360 antigens, selected based on potential relevance to autoimmune disorders, every healthy individual show reactivity towards 1-25 antigens.

Conclusion

Autoantibody profiles in healthy individuals are unique and stable over time.

AUTO1-1031
SHORT ORAL DISCUSSION 6 - PREDICTION, MONITORING AND PREVENTION, PRECISION (PERSONALIZED) MEDICINE IN AUTOIMMUNITY (STATION 2)

TREATMENT ADHERENCE IN RHEUMATOID ARTHRITIS ITALIAN PATIENTS USING A VALIDATED VERSION OF THE 5-ITEM COMPLIANCE QUESTIONNAIRE FOR RHEUMATOLOGY (I-CQR5)

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Background

The 5-item Compliance Questionnaire for Rheumatology (CQR5) allows the identification high adherers (HA) to anti-rheumatic treatment (i.e. taking ≥80% of their medications correctly), or “low” adherers (LA). We previously validated an Italian version of the questionnaire (I-CQR5) following standardized guidelines. The objective was to investigate factors associated with high treatment adherence.

Method

RA patients (disease duration >1 year, undergoing treatment with ≥1 self-administered biological or conventional synthetic disease-modifying anti-rheumatic drugs (bDMARDs, csDMARDs), capable of completing the questionnaire unaided) completed I-CQR5 on one occasion. I-CQR5 were anonymous. To investigate what factors were associated with high adherence, we included demographic and clinical information. Factors achieving a $p<0.10$ in univariate analysis were included in the multivariate analysis.

Results

Among 604 RA patients, 328 patients were enrolled (Fig.1). HA were 35.2% (109/310) of patients. Older age, lower education level, higher prednisone daily dose, use of a csDMARD (particulary hydroxychloroquine and sulfasalazine) and higher patient-VAS were significantly more frequent in LA compared with HA (Fig.1). In the multivariate analysis, bDMARD treatment and employment resulted associated with high adherence: OR 2.88 (1.36-6.1), p=0.006 and OR 2.36 (1.21- 4.62), p=0.012 respectively (Tab.1).

Demographics and clinical variables according to high and low adherence to treatment defined by I-CQR5.

	Total	HA	LA	p value
No.	310	109	201	-
Females (%)	232 (82)	88 (85.4)	144 (80)	0.081‡
Age, years, median (IQR)	57 (48-67)	54 (46-64.8)	59 (49-66)	0.011‡
BMI, median (IQR)	24 (22-28)	25 (23-28)	24 (21-27.3)	0.094‡
Smokers, n (%)	45 (17.2)	13 (16)	32 (17.7)	0.746
Employed, n (%)	127 (44.1)	58 (62.4)	69 (35.4)	p<0.001‡
Education level				0.114
Primary school, n (%)	35 (12.1)	10 (9.4)	25 (13.6)	
Middle school, n (%)	115 (39.7)	35 (33)	80 (43.5)	
Secondary school, n (%)	101 (34.8)	45 (42.5)	56 (30.4)	
University, n (%)	39 (13.4)	16 (15.1)	23 (12.5)	
Primary/middle school education, n (%)	150 (51.7)	45 (30)	105 (70)	0.016‡
Social status				0.921
Living with parents and family	18 (7)	6 (7.5)	12 (6.8)	
Living alone	34 (13.2)	10 (12.5)	24 (13.6)	
Living with partner and family	187 (72.8)	57 (71.3)	130 (73.4)	
Other	18 (7)	7 (8.8)	11 (6.2)	
Positive RF and/or ACPA, n (%)	129 (43.7)	40 (38.5)	89 (46.6)	0.178
Disease duration, years, median (IQR)	12 (7-19)	12 (7.3-18)	11 (6.8-20)	0.876
Fibromyalgia, n (%)	51 (18)	15 (14.6)	36 (20)	0.252
csDMARD treatment, n (%)	165 (54.5)	44 (40.7)	121 (62.1)	p<0.001‡
Methotrexate, n (%)	114 (37.6)	32 (29.6)	82 (42.1)	0.033
Leflunomide, n (%)	31 (10.2)	8 (7.4)	23 (11.8)	0.227
Other csDMARD, n (%)	42 (13.9)	7 (6.5)	35 (17.9)	0.006
bDMARD treatment, n (%)	193 (64.3)	79 (76.7)	114 (57.9)	0.001‡
Treatment duration>24 months, n (%)	178 (79.5)	75 (78.1)	103 (80.5)	0.667
PDN daily dose, median (IQR)	1 (0-5)	1 (0-2.5)	1.5 (0-5)	0.011‡
NSAIDs, n (%)	185 (65.6)	62 (62.6)	123 (67.2)	0.439
Painkillers, n (%)	76 (28.6)	30 (30.6)	46 (27.4)	0.574
Concomitant chronic treatment, n (%)	156 (53.1)	51 (49)	105 (55.3)	0.307
DAS28, median (IQR)	2.3 (1.8-2.8)	2.1 (1.7-2.7)	2.3 (1.9-2.3)	0.088‡
Remission†, n (%)	173 (57.9)	60 (55.6)	113 (59.2)	0.544
Low disease activity¥, n (%)	270 (90.3)	101 (93.5)	169 (88.5)	0.158
Patient - VAS, median (IQR)	30 (10-51)	20 (6-54)	40 (20-56.3)	0.003‡
Physician - VAS, median (IQR)	10 (5-20)	12.5 (1.3-20)	10 (5-20)	0.984
HAQ, median (IQR)	0.5 (0-1)	0.3 (0-1)	0.5 (0.1-1)	0.114
Disease flares, median (IQR)	*44 (31.4)*	*10 (27)*	*34 (33)*	*0.501*
No. of assessments per year, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	0.49
Distance from clinic, km, median (IQR)	30 (11-45)	30 (20-50)	25 (9-45)	0.037‡

†defined as DAS28<2.6; ¥defined as DAS28<3.2; ‡variables included in the multivariate analysis as achieving a p value <0.10 in the univariate analysis.

HA high adherers, *LA* low adherers, *IQR* interquartile range, *BMI* body mass index, *ACPA* anti-citrullinated peptides, *RF* rheumatoid factor, csDMARD conventional synthetic DMARD, bDMARD biological DMARD, *DMARD* disease-modifying anti-rheumatic drug, *PDN* prednisone, *NSAIDs* non-steroideal antinflammatory drugs, *HAQ* Health Assessment Questionnaire, *DAS28* disease activity score in 28 joints, *VAS* visual analogic scale.

	OR (95% C.I.)	p value
Female gender	0.79 (1.58-0.39)	0.501
Employment	2.36 (1.21-4.62)	0.012
bDMARD treatment	2.88 (1.36-6.1)	0.006
Patient-VAS (per 10-unit increase)	0.88 (0.78-1)	0.052
Model constant		<0.001

Conclusion

Only one third of Italian RA patients were highly adherent to treatment. Treatment with bDMARDs and employment status were the major determinants of treatment adherence.

AUTO1-0154
SHORT ORAL DISCUSSION 6 - PREDICTION, MONITORING AND PREVENTION, PRECISION (PERSONALIZED) MEDICINE IN AUTOIMMUNITY (STATION 2)

FREE FIRST MEDICAL ASSISTANCE FOR THE AUTOIMMUNITY NETWORK PATIENTS AFFECTED BY AUTOIMMUNE OR RHEUMATIC DISEASES TRANSITING AT LEONARDO DA VINCI ROME AIRPORT

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Background

The principle of the practice of airport medicine is to bring health to life around the world regardless of our global patients' plans to move or live for a spell elsewhere. Tailored medical assistance for autoimmune or rheumatic patients is not yet a concrete reality even if these patients may well transit at Rome's Airports during their journeys and benefit from our specific skills.

Method

The 24h/7d/365y Rome Airport medical service is open to everyone orbiting around its area for work, holiday or business and therefore a growing figure of just under 10,000 patients during the past 12 months has been taken care of by our department. Focusing on opportunities for partnerships to support passengers with autoimmune diseases, our database of clinical records was analyzed for acute conditions (stable but may detetoriate, urgent care needed, 8.7%)

Results

Among others, acute and recurrent arthritis (0.6%) acute thrombosis or bleeding (2.3%), acute pneumonia / pleurisy and endocarditis (2.3%), type 1 diabetes (1.8%), thyroiditis (1.7%), acute kidney disease (0.6%), fever of uncertain origin (0.5%) and acute chest syndrome (22.5%) might herald a systemic autoimmune disease

Conclusion

Autoimmunity Network patients can be freely and safely assessed and treated during their journeys to ensure their safe travel at the Rome Airport Health and Emergency Unit and may be medically assisted towards the most appropriate clinic by Rome Airport ambulance medical team if needed. On the other hand, those who can recover and may travel will be provided with free reduced-mobility airport service to reach their departure gate

AUTO1-0413
SHORT ORAL DISCUSSION 6 - PREDICTION, MONITORING AND PREVENTION, PRECISION (PERSONALIZED) MEDICINE IN AUTOIMMUNITY (STATION 2)

PERSISTENCE WITH METFORMIN TREATMENT AND ONSET OF RHEUMATOID ARTHRITIS

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Background

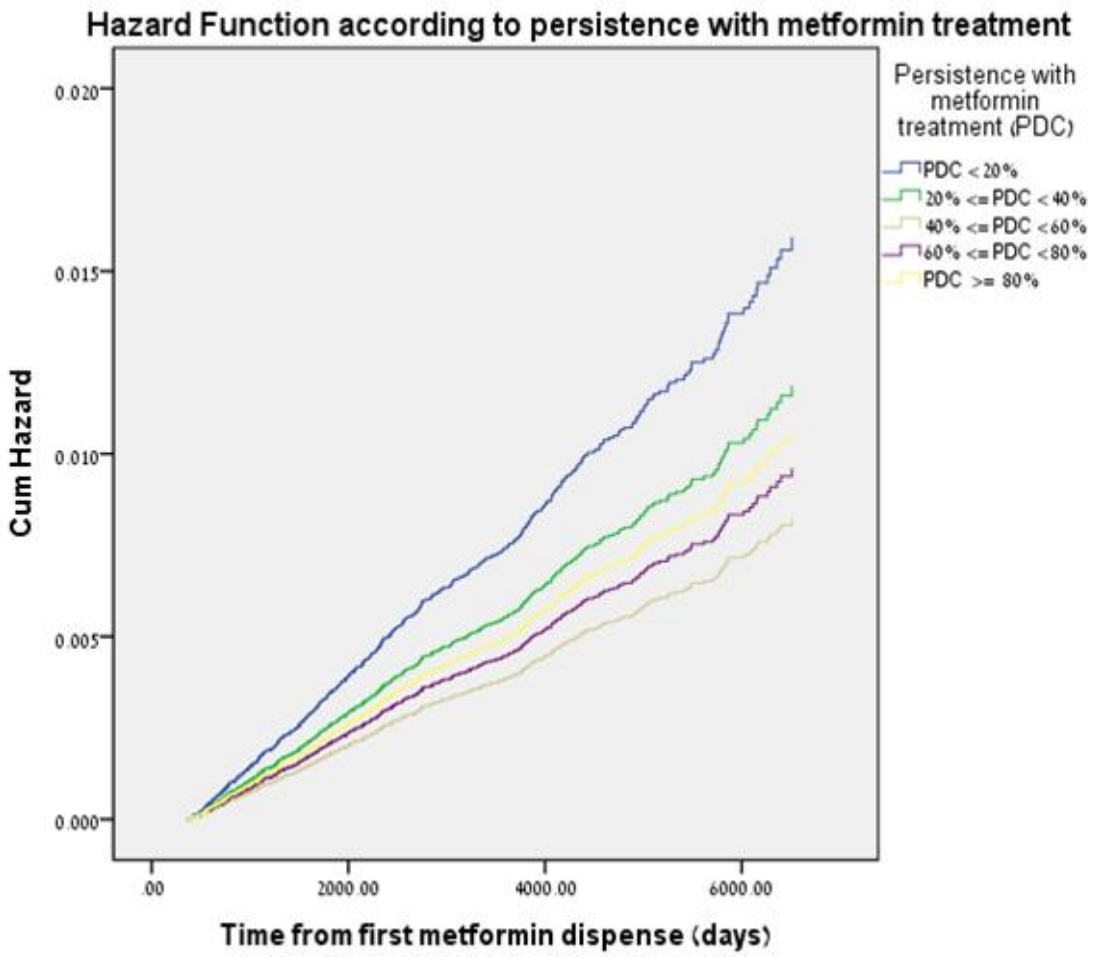
Several studies have suggested that metformin, an oral hypoglycemic agent, possess an anti-inflammatory property and may have a role in the treatment of rheumatoid arthritis (RA), but little is known on its preventive effects.The objective of our study was to examine the association between persistence with metformin and the onset of RA.

Method

Using the computerized database of a large health organization in Israel (Maccabi Healthcare Services, MHS) we have identified incident RA cases among new users of metformin. RA was defined according to physician diagnoses. Participants were followed until the earliest of the following dates: onset of RA, leaving MHS, death, end of follow up (1.1.2016). Persistence with metformin was assessed by calculating the mean proportion of follow-up days covered (PDC) with metformin.

Results

A total of 113,749 eligible patients were included. During the study follow up period (794,386 person-years) we identified 600 incident cases (incidence rate of 75 cases per 100,000 PY). Incidence of RA in women (111 per 100,000 PY) was higher compared to men (42 per 100,000 PY). In a multivariable model, persistence with metformin (PDC≥80%) was associated with lower risk of RA (hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.53-0.82) compared to non-persistent participants (PDC<20%). The figure shows the hazard function according to persistence with metformin treatment. Similar risk reduction was observed among men but did not reach statistical significance (HR=0.85; 95% CI 0.54-1.32).



Conclusion

In the present study, we observed an association between high persistence to metformin therapy and reduced risk of developing RA in women.

AUTO1-0816
SHORT ORAL DISCUSSION 7 - ANTIPHOSPHOLIPID SYNDROME: PAVING THE ROAD (STATION 1)

TOBACCO SMOKE AND AUTOIMMUNITY

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INTRODUCTION
Smoke may influence the immune system and affect the risk and outcome of autoimmune diseases.
OBJECTIVE
To evaluate the role of the exposition to tobacco in autoimmune rheumatic diseases (ARDs).
METHODS
This was an exploratory and self-reported study conducted in 188 women with ARDs namely rheumatoid arthritis (RA, n=51), systemic lupus erythematosus (SLE, n=70), systemic sclerosis (SSc, n=35), and Sjögren's syndrome (SS, n=32). Data were collected by using a structured questionnaire that sought information about demographic and clinical characteristics, clinical outcomes and current or previous exposure to tobacco and wood smoke. In addition, fourteen autoantibodies were measured.
RESULTS
General characteristics of patients are shown in Table 1. Anti-CCP3 levels were significantly increased in those patients with ever tobacco consumption in their lifetime. Ever smoking was associated with higher levels of rheumatoid factor in patients with RA. Interestingly, anti-thyroglobulin antibodies were associated with years of tobacco exposure in patients with SS (Figure 1). Although, an association between exposure to tobacco and autoantibodies reactivity in SSc patients was not found, this exposition was apparently associated with an earlier onset of the disease (p: 0.056).
CONCLUSION
These data confirm the deleterious effect of smoke on the immune system and its influence on ARDs. Further studies exploring levels of cotinine and anti-nicotinic acetylcholine receptor alpha 7 are warranted to further quantified the magnitude of
such an effect.

AUTO1-0909
SHORT ORAL DISCUSSION 7 - ANTIPHOSPHOLIPID SYNDROME: PAVING THE ROAD (STATION 1)

DISCRIMINATION OF APS PATIENTS FROM INFECTIOUS PATIENTS AND ANTIPHOSPHOLIPID ANTIBODY-POSITIVE CARRIERS AND PATIENTS – DOES B2GPI DOMAIN 1 REACTIVITY MATTER?

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Background

Antiphospholipid antibodies (aPL), the serological hallmark of antiphospholipid syndrome (APS), are recommended to be tested by ELISA. However, ELISA can detect aPL in apparently healthy subjects (aPL-positive [aPL+] asymptomatic carriers, infectious disease patients and APS-asymptomatic patients with systemic autoimmune rheumatic diseases (SARD). A novel aPL line immunoassay (LIA) was designed to address this issue.

Method

Ninety-five APS patients, 158 controls (41 aPL+ SARD patients without thrombotic events, 44 aPL+ asymptomatic carriers, infectious-disease controls) were analyzed by a multiplex LIA for the detection of aPL to cardiolipin (CL), phosphatic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol (PG), phosphatidyl-inositol, phosphatidylserine, beta2-glycoprotein I (β2GPI), prothrombin, and annexin V for aPL reactivity. Samples have been also tested by anti-CL and anti-β2GPI ELISAs and Lupus Anticoagulant assay as well as anti-β2GPI Domain 1 (D1) and 4-5 (D4-5) assays.

Results

Monoclonal antibodies against D1 (MBB2, HCAL) recognized β2GPI bound to LIA-matrix and β2GPI of the specimens under investigation in anionic PL-complexes. LIA appeared to favor the detection of anti-D1-ß2GPI antibodies. Comparison of LIA with criteria aPL-assays revealed good agreement. However, IgG binding to CL and ß2GPI in LIA was significantly lower in aPL+ carriers and VDRL+ samples than in APS patients in contrast to ELISA. The ratio of D1/D4-5 reactivity demonstrated the best performance for the discrimination of APS patients from SARD patients with no thrombotic events which was similar to the performance of anti-PG IgG by LIA.

Conclusion

aPL-profiling by LIA exposing preferably D1-β2GPI can aid in differentiating APS from infectious disease patients, APS-asymptomatic SARD patients and asymptomatic carriers.

AUTO1-1055
SHORT ORAL DISCUSSION 7 - ANTIPHOSPHOLIPID SYNDROME: PAVING THE ROAD (STATION 1)

NEUROLOGICAL MANIFESTATIONS IN PRIMARY ANTIPHOSPHOLIPID SYNDROME

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Background

Primary antiphospholipid syndrome (pAPS) is an isolated systemic autoimmune disease, classically characterized by thrombotic events and/or pregnancy related morbidity. Its central nervous system involvement can be thrombotic (t-pAPS - stroke, TIA, Sneddon syndrome, and cerebral venous thrombosis) or non-thrombotic (nt-pAPS - epilepsy, headaches, movement disorders, myelitis, and neuropsychiatric deficits).

Method

A retrospective analysis of 73 pAPS patients from Neurology and Immunology outpatient clinic of a tertiary hospital was performed.

Results

Neurological manifestations were reported in 53 patients (72.6%), 37 of them were women (69.8%) and the mean ages at pAPS diagnosis and at neurological manifestation onset were 46years±14 and 43years±14, respectively. The most frequent neurological manifestation was ischemic stroke (41.5%) and the least was chorea (3.8%). Two subgroups were compared, t-pAPS (67.9%) and nt-APS (32.1%) and were similar regarding to gender, age at onset, titles of antiphospholipid antibodies, event recurrence and outcome. Vascular risk factors (88.9%vs.52.9%, p=0.011) and cognitive dysfunction (41.7%vs.11.8%, p=0.029) were more prevalent in t-pAPS, while myelitis (8.3%vs.41.2%, p=0.008) and ocular symptoms (5.6%vs.47.1%, p=0.001) were more prevalent in nt-pAPS. Hypocoagulation rates were not significantly different between subgroups (69.4%vs.43.8%, p=0.079), but there is a tendency to start hypocoagulation more promptly in the t-pAPS.

Conclusion

In our cohort, patients with thrombotic compared with non-thrombotic p-APS with neurological manifestations had distinct features regarding frequency of vascular risk factors, cognitive dysfunction, myelitis, and ocular symptoms. The underlying pathophysiology of nt-pAPS events is yet to be fully elucidated. Even though no standard treatments are currently available for non-thrombotic manifestations, in clinical practice hypocoagulation is frequently used.

AUTO1-1050
SHORT ORAL DISCUSSION 7 - ANTIPHOSPHOLIPID SYNDROME: PAVING THE ROAD (STATION 1)

ANTIPHOSPHOLIPID ANTIBODIES – INDEPENDENT PRO-ATHROGENIC PARTICLES

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Background

Atherosclerosis is the most common pathological process affecting the artherial wall is known that a number of congenital and acquired factors are involved in this process, such as lipid status, BMI, arterial hypertension, and the presence of harmful habits.

Method

We evaluated the ultrasonographic, atherosclerotic changes of the carotid arteries ot 57 APS patients, 41 SLE and 41 healthy controls.

Results

From descriptive statistics, it is clear that patients with the highest median values of intima-media are those belonging to the APS group. With the Kruskall-Wallis analysis, we found a statistically significant difference in IMT between the study groups for left ($p = 0.005$) and right ($p = 0.014$) carotid arteries.
Comparative analysis between the groups showed that the pathological IMT (> 900 μm) pathways in the right carotid artery were for patients with antiphospholipid syndrome 15 (26.3%). In healthy controls, 3 (7.3%) were found, and SLE patients did not experience such cases. Similar data are for left carotid artery (LCCA).
We compared the intimate media scores between the Chi-square test groups by establishing a statistically significant correlation for the two carotid arteries - IMT-RCCA $p = 0.001$ for IMT-LCCA $p = 0.002$.

Conclusion

In our study we found that the APS is associated with hier values of the IMT in carotid artheries, compared to SLE patients ant healthy controls.

AUTO1-0691
SHORT ORAL DISCUSSION 8 - CANCER AND AUTOIMMUNITY (STATION 2)

SYSTEMIC AND AUTO-IMMUNE DISEASES ASSOCIATED WITH LARGE GRANULAR LYMPHOCYTE LEUKEMIA: DIAGNOSTIC PATH AND SYNDROMIC CHARACTERIZATION IN INTERNAL MEDICINE

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Background

Large granular lymphocyte leukemia (LGLL) may be associated with systemic and/or auto-immune diseases (SAIDs) in hematologic series. This study aimed to describe the spectrum of SAIDs reviewed in Internal Medicine in a cohort of consecutive patients with LGLL.

Method

We conducted a monocentric retrospective study of patients followed for LGLL in the department of internal medicine in the Caen university hospital, from 1999 to 2016. LGLL was evidenced either on demonstration of clonality on TCR/KIR study, or on two immunophenotypings. A complete work-up ruled out any malignancy or infection. Autoimmune serologies were obtained for all patients.

Results

Sixty-three patients (median age: 75-years) with LGLL (T, NK, or T/NK types, in 81, 16 and 3%, respectively) were included. In 18% of them, LGLL was non-symptomatic and no SAID was diagnosed. In 38% of patients, LGLL was associated with a well-defined SAIDs, including rare conditions such as cryoglobulin-associated vasculitis, giant cell arteritis or bradykinin angioedema. In the remaining 44% of patients, inflammatory clinical and biological abnormalities were observed, without enough evidence to be classified as a well-defined SAIDs. Lymphocytosis and tumoral presentations were observed in 40% and 21% of patients, respectively, which is less than observed in hematological series. Conversely, when compared to the published literature, we found a higher rate of SAID or unclassified inflammatory diseases.

Conclusion

Our study confirms that LGLL is often associated with SAIDs, especially with their unclassified forms. Prospective collaborative studies are required to better characterize the spectrum of both entities.

AUTO1-0997
SHORT ORAL DISCUSSION 8 - CANCER AND AUTOIMMUNITY (STATION 2)

AUTOIMMUNITY, DIFFUSE LARGE B-CELL NON-HODGKIN LYMPHOMA AND AL AMYLOIDOSIS: A RARE ASSOCIATION

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Background

Systemic autoimmune disorders are increasingly recognized as risk factors for lymphoma. Amyloid A (AA) amyloidosis arises as a complication of several chronic inflammatory conditions, namely autoimmune and lymphoproliferative diseases. Contrary, amyloid light-chain (AL) amyloidosis is a rare complication of connective tissue diseases or lymphomas.

Method

A 58-year-old female, with mixed connective tissue disease and antiphospholipid syndrome, was admitted with oropharyngeal swelling, adenomegaly and weight loss in the last three months. Physical examination revealed ulcerated right tonsil, right supraclavicular, axilar and inguinal enlarged lymph nodes. Blood tests showed an increased β2-microglobulin and hypogammaglobulinemia. Body CT-scan revealed solid masses with 5 x 4 cm in right supraclavicular, axilar and inguinal regions. Tonsil, supraclavicular and axillar lymph node biopsies revealed diffuse large B-cell lymphoma non-germinal center, EBV negative. The patient started treatment with R-CHOP.

Results

Throughout clinical workup, upper digestive endoscopy revealed antral gastritis with bulboduodenitis. Unexpectedly, biopsies were positive for non-AA amyloid substance. Thus, the hypothesis of AL amyloidosis was considered. Bence Jones proteinuria was detected and cardiac MRI confirmed infiltrative cardiomyopathy. Although neither cardiac nor kidney biopsies were performed (due to oral anticoagulation), AL-amyloidosis in the context of lymphoproliferative and systemic autoimmune diseases was assumed and bortezomib was started with complete disease remission.

Conclusion

Unlike AA amyloidosis, AL amyloidosis is rarely described in non-Hodgkin lymphoma, as well as in systemic autoimmune diseases. The authors present a case of AL amyloidosis in the context of systemic autoimmune disease and non-Hodgkin lymphoma, a rare association raising interesting questions about the etiopathogenic link of the different entities.

AUTO1-0078
SHORT ORAL DISCUSSION 8 - CANCER AND AUTOIMMUNITY (STATION 2)

FETAL SEQUENTIAL MULTIORGAN AUTOIMMUNITY ASSOCIATED WITH RECURRENT POST THYMECTOMY THYMOMA

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Background

Autoimmune disorders are a clinical hallmark of thymoma. However, the development of various autoimmune diseases after thymectomy is quite common.

Method

We described the sequential presence of multiorgan autoimmunity involving intestine, myasthenia gravis, skin, alopecia areata and erythroderma occurring in a patient with recurrent post thymectomy thymoma. We also made a literature review.

Results

The patient was treated with oral prednisone(50mg), azathioprine(100mg) daily, narrow-band UVB therapy and topical steroids, with no clinical response. Immunosuppressive therapy was changed to tacrolimus(3mg) daily. The lesions and diarrhea cleared after 8 month therapy with stable thymoma and myasthenia gravis. The prednisone was tapered slowly. Severe alopecia areata(alopecia totalis) was developed 9 months later Unfortunately, the patient lesions recurred and deteriorated to erythroderma 13 months succeeding the recurrent thymoma. The patient died of sepsis 8 months after erythroderma. In this case, thymoma’s recurrence can trigger overlapping autoimune diseases

Conclusion

Literature review suggested that cutaneous involvement of TAMA could be a terminal condition of thymoma[8]. Including our case, 15 of 18 cases with erythroderma resulted in a fatal course. GVHD-like erythroderma is a fatal sign of paraneoplastic phenomenon.

AUTO1-0510
SHORT ORAL DISCUSSION 8 - CANCER AND AUTOIMMUNITY (STATION 2)

CHARACTERISTICS OF CANCERS IN PATIENTS WITH SYSTEMIC SCLEROSIS : A CLOSE TEMPORAL RELATIONSHIP WITH BREAST CANCER ONSET

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Background

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder with multisystem involvement, vasculopathy and fibrosis. SSc is associated with an increased risk of malignancy and in a subgroup of patients, SSc appears to be an immune response agaisnt cancer. Herein, we aimed at describing the malignancies in SSC patients from our institution.

Method

We conducted a retrospective study at the Montpellier University Hospital and included SSc patients followed between 2003 and 2017.

Results

We identified 55 patients with SSc, and at least one cancer. The main malignancy subtypes were breast (n=21), lung (n=9), gastrointestinal (n=8), skin (n=8) and haematological (n=6). Among SSc patients with cancer, 30.2% were positive for anticentromere antibodies, 22.6% were positive for anti-Scl-70 antibodies. In this retrospective study, robust data on anti-RNA polymerase III antibodies are lacking, but cancer seemed to be temporally associated with centromere- and Scl70-negative patients. Fifteen patients had cancer within three years following or prior to diagnosis of SSc. Among them, ‘concommittant’ breast cancer was the most common (n=7/15). Concerning the evolution of breast cancers, four patients (n=4/7) had early onset metastases. Lung cancers appeared later in the course of SSc.

Conclusion

Our study confirms several data from the literature. Breast and lung cancers seem to predominate in SSc patients with different temporality. A close temporal relationship between SSc and breast cancer was found, which strengthens the hypothesis of a pathophysiological link between these two diseases.

AUTO1-1041
SHORT ORAL DISCUSSION 8 - CANCER AND AUTOIMMUNITY (STATION 2)

INFLAMMATORY MYOPATHIES. A PRIMARY OR SECONDARY CONDITION?

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Background

Inflammatory myopathies (IM) are rare and often associated with other diseases such as cancer and systemic autoimmune diseases. The association with celiac disease is well established.

Method

Internal Medicine Consultation case

Results

A 48-year-old woman with a family history of breast cancer was diagnosed in 2009 with anaemia. Endoscopy with jejunal biopsy showed lymphocytic infiltration compatible with type 1 celiac disease. HLA DQ2 allele was positive. Anti-tissue transglutaminase antibody and anti-gliadin were negative. The patient complained of proximal myalgias. On physical examination she had painful proximal muscular oedema. There were no signs of vasculitis or cutaneous lesions. Blood results: Hb 12,6g/dL, ESR 100mm, normal kidney function, LDH 470 U/L, aldolase 14,8 U/L, polyclonal gammopathy, and normal urinalysis. ANA screening: anti-Jo1 was positive, remaining autoimmunity was negative. Mammography and colonoscopy were normal. Full-body CT scan showed hepatic steatosis and uterine myomas. A gluten free diet was recommended without compliance. Clinical improvement was noticeable with prednisolone, 20mg/day. With steroids tapering she had a relapse and methotrexate was added with clinical improvement. Periodic mammograms were normal. In 2015, at age 54, a control mammography showed bilateral breast cancer. She was treated with tamoxifen after double mastectomy with oophorectomy. Paraneoplastic myopathy was assumed. In 2016, methotrexate was stopped due to liver fibrosis, without significant relapse. She has no signs of myositis after 3 years.

Conclusion

We present a case of inflammatory myopathy initially ascribed to celiac disease that 6 years later appears strongly related to breast cancer. This case underlines the association of myopathies with cancer.

AUTO1-0951
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

EFFECT OF INTERFERON ALFA-2A ON PERIPHERAL BLOOD T REGULATORY AND T HELPER 17 CELLS IN PATIENTS WITH BEHÇET UVEITIS RESISTANT TO CONVENTIONAL IMMUNOMODULATORY THERAPY

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Background

Behçet uveitis (BU) is characterized by relapsing-remitting non-granulomatous panuveitis attacks with occlusive retinal vasculitis. Interferon alfa-2a (IFNα-2a) has been shown to be efficacious in BU. The objective of the study is to assess phenotypical and functional effect of IFNα-2a on circulating Tregs and Th17s in BU.

Method

Twenty-one patients with active BU resistant to conventional immunomodulatory therapy and age-/sex-matched controls were recruited. Blood samples were collected before initiation of and after clinical and angiographic remission was achieved with IFNα-2a. Treg and Th17 percentages were determined as CD3+CD4+FoxP3+ and CD3+CD4+IL17A+ by flow-cytometry. After *in vitro* Treg and Th17 stimulation, cytokine release was determined by ELISA.

Results

Mean CD4+FoxP3+ cell percentage was significantly higher in patients than in controls (6.79±0.24 vs 2.47±0.06) and decreased significantly after IFNα-2a therapy (2.92±0.17), ($p<0.001$). Mean IL-10 concentration (pg/mL) in patients' Treg culture supernatant was significantly lower than controls (4.26±0.28 vs. 5.15±0.32) and increased significantly with IFNα-2a ($p<0.05$). After *in vitro* stimulation, CD4+IL17A+ cell percentage was significantly higher in patients than in controls (33.46±0.95 vs 13.75±0.72) and decreased significantly after IFNα-2a (13.34±1.26), ($p<0.001$). Mean IL-17A (382.82±28.26 vs. 273.44±35.16), IL-21 (529.03±89.75 vs. 303.19±52.20), IL-22 (1520.78±98.58 vs. 1024.84±117.88), IL-23 (32.89±5.17 vs. 20.32±5.51), and IFN-g (405.92±29.34 vs. 309.86±31.38) concentrations (pg/mL) in patients' Th17 culture supernatant were significantly higher than controls and decreased significantly with therapy ($p<0.05$).

Conclusion

Despite an increase in Tregs impaired IL-10 production suggests Treg dysfunction in patients with active BU. IFNα-2a recovers Treg function, induces IL-10 production from Tregs, and suppresses Th17s.

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AUTO1-0986
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

THE MICROBIOME AND AUTOIMMUNE DISEASES: “FRIENDS OR FOES”?

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Background

The microbiome is represented by microorganisms which live in a symbiotic way with the mammalian. The microorganisms have the ability to influence different physiological aspects such as the immune system, metabolism and behaviour. The presence of the microbiome and the microbial products (i.e. butyrate, PSA, SCAFs) can regulate the development and function of the immune system in the host. There is “a close dialogue” between bacteria and host immune system, through pattern recognition such as Toll-like receptor (TLRs) on the membrane of the immune and epithelial cells. Alterations of the microbiome (dysbiosis) can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens.The dysbiosis can induce the loss of tolerance in immune system and thus activation of the immune system’s cells. It is now clear that alterations of the microbiome in subject with certain genetic background or exposed to environmental factors, can underlay the pathogenesis of the autoimmune diseases.

Method

An alteration of the intestinal flora (lower *Firmicutes/Bacteroidetes* ratio) is described in patients with lupus. Moreover, changes in the gut commensal and periodontal infection disease are proposed as important factors for the pathogenesis of rheumatoid arthritis and other autoimmune diseases.

Results

The microbial supplements (probiotics, diet or prebiotics), already known in paediatric and general medicine, have been shown to decrease inflammatory activity restoring the gut flora.

Conclusion

Nevertheless, the role of the microbiome in autoimmune disease is not completely understood. Further studies will be necessary to clarify the importance of the commensal microorganisms.

AUTO1-0396
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE) PATIENTS' NEUTROPHILS ARE HIGH IN STIMULATORS AND ACTIVATORS OF PHAGOCYTOSIS

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Background

The multisystem autoimmune disease JSLE is characterized by production of autoantibodies. These develop when phagocytosis is dysregulated leading to exposure of nuclear antigens, for example from Neutrophil Extracellular Trap formation (NETosis). Previous studies have focused on the effect of serum on phagocytosis, rather than neutrophils. We investigated expression of phagocytosis receptors including TLR2, complement receptor (CR3) and FcγRIIIb, and S100A9 as a stimulator of phagocytosis as well as the ability of JSLE neutrophils to phagocytose.

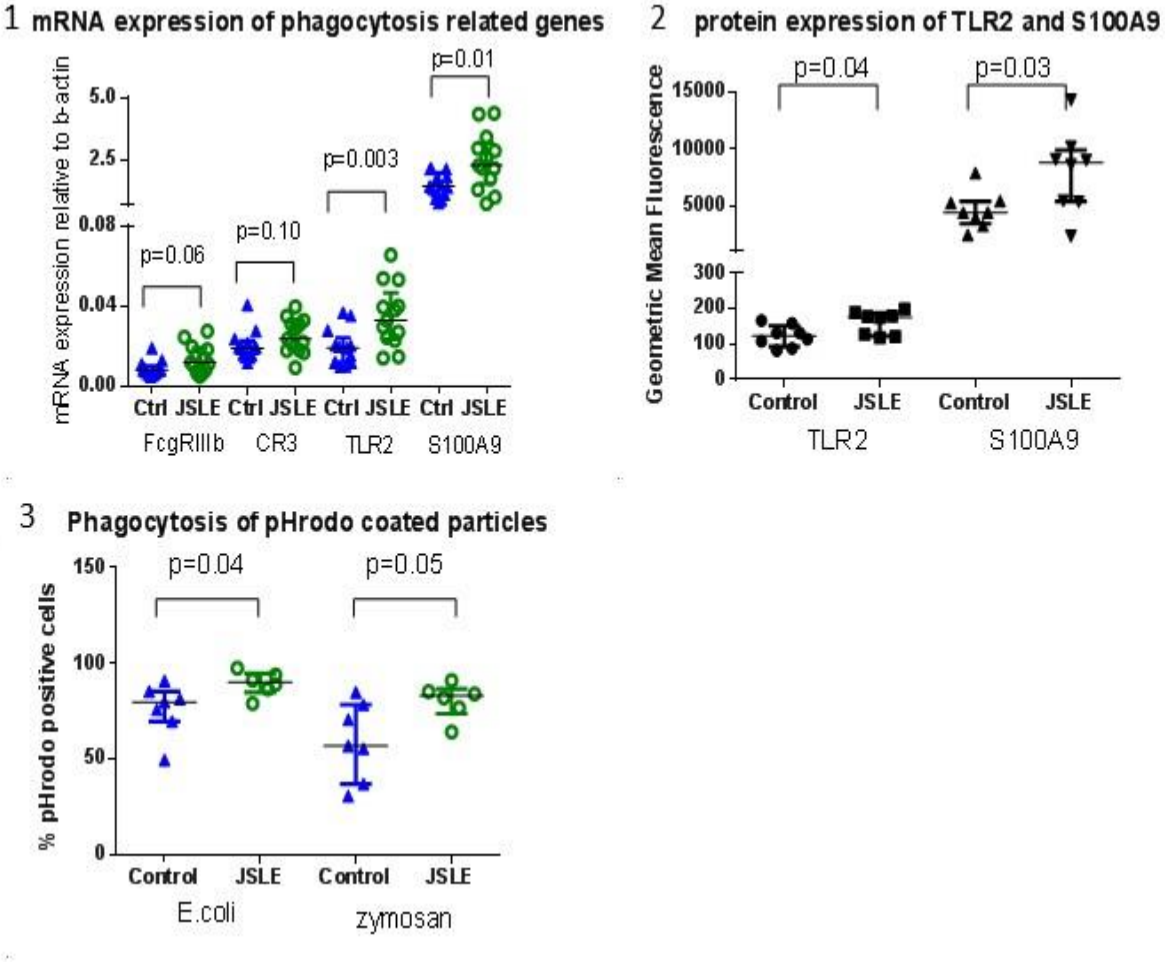
Method

Neutrophils of JSLE patients (diagnosed <17 years of age) and paediatric healthy controls were isolated from whole blood. The mRNA expression of beta-actin (internal standard), TLR2, CR3, FcγRIIIb, and S100A9 in JSLE patients (n=13) and paediatric healthy controls (n=13) were measured using qPCR. TLR2 and S100A9 protein levels were measured by flow cytometry. For functional analyses of phagocytosis, neutrophils were incubated with fluorescently labelled *E.coli* and zymosan particles and control serum, and analysed using flow cytometry.

Results

In JSLE patients compared to controls we found: (Figure 1) mRNA of TLR-2, CR3, FcγRIIIb and S100A9 was increased, significantly so for TLR2 and S100A9 ($p<0.05$); (Figure 2) a significant increase of TLR2 and S100A9 protein expression ($p<0.05$);

(Figure 3) increased phagocytic ability using functional analyses (p≤0.05).



Conclusion

Our data demonstrate that JSLE neutrophils have high concentrations of activators of phagocytosis but indicate no impairment of phagocytic function. Previous studies demonstrate JSLE serum may inhibit phagocytosis. Highly activated neutrophils, primed to phagocytose, may be substantially dysregulated by factors present in the environment.

AUTO1-0914
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

T FOLLICULAR HELPER CELLS PTOMOTE SALIVARY DYSFUNCTION VIA ELICITING AUTOREACTIVE B CELL RESPONSE IN EXPERIMENTAL SJOGREN'S SYNDROME

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Background

Primary Sjögren's syndrome (pSS) is characterized by lymphocytic infiltration and tissue destruction of exocrine glands including salivary glands (SG), but the immunopathogenic mechanisms underlying the salivary dysfunction remain partially understood. Here we aim to investigate the role of T follicular helper (Tfh) cells in the pathogenesis of SS.

Method

The experimental SS (ESS) was induced in normal mice as we previously reported (Lin X, et al. Annals of the Rheumatic Diseases, 2015; 74:1302-10). Both saliva flow rates and histological analysis of SG were performed to evaluate disease onset and tissue pathology. Various T and B cell subsets in draining cervical lymph nodes (CLN) and spleen were analyzed by flow cytometry. ESS mice were immunized with synthesized M3 muscarinic receptor (M3R) peptide for generating antigen-specific Tfh cells.

Results

Increased PD-1+CXCR5+ Tfh cells were detected in peripheral blood and CLN, which were closely correlated with elevated serum levels of anti-M3R muscarinic autoantibodies and SG tissue damage during ESS development. Moreover, Tfh cells were detected among the glandular infiltrates in ESS mice by immunofluorescent microscopy. Notably, intravenous injection of purified serum IgG from anti-M3R seropositive ESS mice and pSS patients resulted in significantly decreased saliva secretion in NOD/SCID mice. Furthermore, transfer of M3R-specific Tfh cells resulted in markedly enhanced germinal center B cell reaction and increased anti-M3R IgG production with accelerated salivary hypofunction in ESS mice.

Conclusion

Together, our findings have demonstrated that Tfh cells play a critical role in eliciting autoreactive B cell response and contribute to salivary dysfunction during SS development.

AUTO1-0991
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

CYTOKINES AND SOLUBLE RECEPTORS OF THE IL-1 FAMILY IN SCHNITZLER SYNDROME

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Background

Schnitzler syndrome (SchS) is an autoinflammatory disorder characterized by chronic urticaria, fever and monoclonal gammopathy. The success of IL-1 blocking therapies suggests a crucial role of IL-1 in disease induction. The aim of this study is to perform a comprehensive analysis of IL-1 family cytokines and soluble receptors in a group of SchS patients.

Method

Three patients fulfilling the criteria for the diagnosis of SchS were recruited; 86 blood donors formed the control group.

Cytokines of the IL-1 family (IL-1a, IL-1b, IL-33, IL-18), soluble receptors (sIL-1R1, sIL-1R2, sIL-1R3, sIL-1R4) and antagonists (IL-1Ra, IL-18 binding protein -IL-18BP) were measured by a multiarray ELISA assay. Free IL-18 was calculated as the amount of IL-18 not inhibited by IL-18BP.

Cytokine levels were compared by Mann Whitney test.

Results

IL-18 and free IL-18 were increased in patients *vs*. controls (p=0.005 and p=0.0082, respectively), while IL-18BP levels were not different. The serum levels of IL-1a, IL-1b and IL-33 were undetectable in both patients and controls. The soluble receptors sIL-1R1, sIL-1R2 and ST2/sIL-1R4, and the IL-1 antagonist IL-1Ra were all within the normal range; sIL-1R3 levels were significantly lower in patients *vs*. controls (p= 0.039).

Conclusion

The data indicate that SchS is characterized by increased circulating levels of free IL-18, possibly leading to a higher activation of innate/inflammatory effector cells.

At variance with other inflammatory diseases, the lack of increase in sIL-1R1 and sIL-1R2 and the decreased levels of sIL-R3 imply a failure in the counterbalancing mechanism aimed at inhibiting excessive IL-1b in the tissues.

AUTO1-1048
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

HERPES ZOSTER IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background

Immunomodulating drugs radically changed the treatment of autoimmune diseases, however they also increase the risk of infectious disease. Herpes Zoster (HZ) is caused by the reactivation of the varicella-zoster virus (VZV), when a decrease in the effectiveness of the cellular immune responses occurs, due to age, disease, or drugs.

Method

Case description: A 32 years old woman followed in clinic with systemic lupus erythematosus (SLE) with malar erythema, polyarthralgias, cutaneous vasculitic lesions and class IV lupus nephritis.

Results

Laboratory showed antidsDNA 1310 UI/ml, ANA 1/640 with positive antihistone antibody, complement consumption, urinary proteinuria of 2,8g/24h and erythrocyte sedimentation rate 22 mm. She was taking prednisolone 0,5mg/kg/weight/day (PDN), mycophenolate mofetil (MMF) 3 g/day and hydroxychloroquine (HCQ) 400 mg /day. She presented with vesiculobullous lesions on the back, breast and inferior left limb. Cutaneous disseminated HZ was diagnosed and Acyclovir EV treatment started with clinic improvement. Paralysis and paresthesia of the inferior left limb ensued with absent reflexes compatible with periferic neuropathy.

Conclusion

This case presents an extensive and atypical HZ infection, complicated with neuropathy, in a young women with SLE under immunosuppressive therapy combined with steroids, which could increase the incidence and gravity of the HZ infection. This case illustrates the challenges of SLE treatment and the necessity of prophylaxis to avoid future reactivation of HZ. It reminds us of considering HZ vaccination, previously to the beginning of immunosuppressive therapy. More studies are still necessary to define the best management and treatment to this particular kind of patients.

AUTO1-1035
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

CHARACTERIZATION OF INTESTINAL ENTEROBACTERIAL MICROBIOME OF CHILDREN WITH GENETIC SUSCEPTIBILITY FOR TYPE 1 DIABETES BY ENHANCED MICROBE ENRICHMENT METHOD

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Background

Approximately 40% of type 1 diabetes (T1D) can be explained by high risk HLA class II alleles (Couper, 2001), hence the impact of environmental factors remains high. Pellegrini et al. (2017) discovered specific abnormalities in inflammatory profile and microbiota of duodenal mucosa in patients with T1D compared to control subjects and patients with celiac disease. In this pilot study family *Enterobacteriaceae* bacteria of the duodenal microbiome of infants with genetic susceptibility to T1D were characterized.

Method

Portable Microbe Enrichment Unit (PMEU; Finnoflag Oy, Kuopio and Siilinjärvi, Finland) (Hakalehto, 2012) was used for characterization of enterobacterial microbiome from fecal samples collected from infants at different ages (Pesola and Hakalehto, 2011; Pesola et al., 2009). Direct plate culture on BBL™ CHROMAgar™ Orientation (Becton, Dickinson & Company, New Jersey, USA) was compared with plate culture performed after pre-enrichment of the samples in the PMEU. Phenotypic comparison of isolates was performed by PhenePlate™ – RS (Bactus AB, Huddinge, Sweden).

Results

2,6-fold amount of enterobacterial phenotypes were detected from pre-enriched samples compared to parallel directly plated samples (Pesola and Hakalehto, 2011). Balanced existence of both mixed acid fermenting and 2,3-butanediol producing enterobacterial isolates was recognized (Hakalehto et al., 2008) with interesting variations among individuals.

Conclusion

Based on the results of this and earlier studies, the PMEU method provides tools for personalized medicine based on the analysis of the intestinal microbiome (Hakalehto, 2012). It can be used for monitoring dynamics of the microbiome of individuals at risk of T1D and other autoimmune diseases.

AUTO1-0973
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

AN ELEVATED TRIVIAL INFECTION PEAK EVENTS CHARACTERIZES FIRST-DEGREE RELATIVES DEVELOPING RHEUMATOID ARTHRITIS

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Background

The aim of this study was to characterize infection events in a longitudinal cohort of first degree relatives (FDR) of probands with rheumatoid arthritis (RA) and explore associations with RA development.

Method

FDR individuals (n=310, mean follow-up of 9 years) including 26 who have developed RA (incidence: 9.1 cases/1,000/year) and age-matched healthy women without familial RA history were ascertained from the 1997-2017 women Tatarstan cohort.

Results

When compared to healthy women and at first examination, FDR individuals were characterized by an elevated annual rate and/or duration of trivial infections (e.g. upper respiratory tract infection symptoms, herpes simplex virus reactivations, and tonsillitis) and skin infections. For those who developed RA they were characterized by a higher morning stiffness and non-erosive arthritis, RF and anti-CCP2 Ab positivity, and an annual increase in trivial infection events that started in the three years preceding RA onset, and thereafter decreased following RA treatment initiation with DMARDs. In addition, it was observed that granulocyte reactive oxygen species (ROS) production that plays a crucial role in controlling infections was quantitatively [STZ peak and its area under the curve (AUC)] and qualitatively (STZ time of peak) altered in FDR, and even more at RA diagnosis. In untreated early RA patients, a positive correlation exists between disease activity and STZ-dependent ROS production.

Conclusion

An annual increase of trivial infection events that may result from an inappropriate immune response should be considered as an independent environmental factor associated with RA development during the management of FDR at pre-clinical stage.

AUTO1-0878
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

ANTIBODY RESPONSES AGAINST HUMAN CYTOMEGALOVIRUS ANTIGENS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background

A meticulous assessment of simultaneous ab reactivity to most immunogenic human cytomegalovirus (HCMV) proteins has never been done in patients with diffuse systemic sclerosis (dSSc) or limited (lSSc).

Aim: To assess the clinical significance of abs against a wide range of HCMV antigens.

Method

Sera from 91 SSc patients (48 lSSc/43 dSSc) and 32 demographically matched healthy controls (HC) tested for IgG anti-HCMV abs (whole extract) by ELISA. IgG abs against individual UL57, UL83, UL55, UL44, p38, UL99 and other subdominant antigens were tested by immunoblotting using whole HCMV extract.

Results

Anti-HCMV abs by ELISA were detected in 85 (93.4%) SSc patients compared to 29 (90.6%) HC (SSc *vs* HC, *p*=ns). Within anti-HCMV positive SSc, the most prevalent antibodies were anti-UL57 (91.2%), anti-UL99 (69.2%), anti-UL83 (59.3%) and anti-UL55 (47.6%). Anti-UL55 abs tended to be more frequent in SSc (lcSSc or dcSSc) than HCs. Anti-UL57 levels were significantly higher in SSc or SSc subtypes than HCs. In contrast, anti-p38 levels were lower in lSSc than HCs. Anti-UL83 abs were more frequent in SSc with pulmonary fibrosis compared to those without (*p*=0.050). No other clinical associations were found.

Conclusion

This is the first comprehensive analysis of anti-HCMV ab responses in patients with SSc. Our study shows that though ab responses amongst SSc patients and healthy controls are largely comparable when extracts of CMV are used as antigenic source, several differences are found when antibody reactivities to specific antigens are tested some bearing clinical significance.

AUTO1-0436
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

EXPRESSION OF ciRS-7 IN RHEUMATOID ARTHRITIS PATIENTS

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Background

A recent analysis revealed that thousands of mammalian circular RNAs (circRNAs) harbor miRNA response elements (MREs), suggesting a potential role as competitive endogenous RNAs (ceRNAs). Recent studies have demonstrated that ciRS-7 (circular CDR1 antisense), which acts as a powerful miR-7 sponge, contains more than 70 putative binding sites for miR-7 and may inhibit its target genes.

Method

The aim of this study was to investigate the expression of ciRS-7 in peripheral blood mononuclear cells (PBMCs) from patients with rheumatoid arthritis (RA) as well as the correlation between ciRS-7 and the target genes of miR-7.

Results

We found that ciRS-7 was significantly increased in RA patients and could potentially differentiate the RA patients from healthy controls. Additionally, the expression of mTOR, one of the miR-7 target genes, had positive and negative relationships with ciRS-7 and miR-7 expression, respectively. Notably, the relative expression of miR-671, which mediated the regulation of circular CDR1 antisense homeostasis, was significantly decreased in RA patients.

Conclusion

Thus, downregulated miR-671 may influence the level of ciRS-7 in RA patients, and enhanced ciRS-7 could inhibit the function of miR-7 and further relieve the inhibitory effect of miR-7 on mTOR.

AUTO1-0736
SHORT ORAL DISCUSSION 9 - INFECTION, MICROBIOME AND IMMUNOMODULATION (STATION 1)

RED BLOOD CELLS OXIDATIVE STRESS AND SENSITIVITY OF PERIPHERAL BLOOD MONONUCLEAR CELLS IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS ARE MODULATED WITH ALFACALCIDOL

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Background

Oxidative stress plays a significant role in pathogenesis of autoimmune diseases including rheumatoid arthritis (RA). Hormone D and its analogues show immunomodulatory activities that provide a beneficial effect in immunoinflammatory diseases.

Method

The aim of this study was to assess the effect of alfacalcidol treatment on superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activity and .glutathione (GSH) and malondialdehyde (MDA) levels in patients with active RA Sixteen patients with active RA and twenty controls were consecutively enrolled in the study. Blood samples were taken before and after 12 weeks of alfacalcidol therapy (2μg/day). Disease activity was assessed using DAS28 score.

Results

The alfacalcidol treatment, significantly (p=0.04) reduced SOD activity in RA patients to levels obtained in controls. CAT activity in RA patients was significantly decreased after therapy (p=0.001). Moreover, post treatment CAT activity was significantly lower compared to controls (p=0.000). The activity of GPx was significantly lower in RA patients before treatment, compared to controls (p=0.04). After therapy, GPx activity was restored to control levels. GSH levels were significantly higher in RA patients before treatment, compared to controls (p=0.03). Alfacalcidol therapy significantly reduced GSH levels (p=0.01) as well as MDA levels in RA patients (p=0.19). Moreover, 12-weeks alfacalcidol therapy, modulated the response of RA patients' PBMC to stimulation preventing the O_2^- production and mitochondrial membrane depolarisation. After alfacalcidol treatment, significant clinical improvement was observed.

Conclusion

Twelve weeks treatment with alfacalcidol moderated activity of antioxidant enzymes and resulted in significant reduction of disease activity in RA patients.