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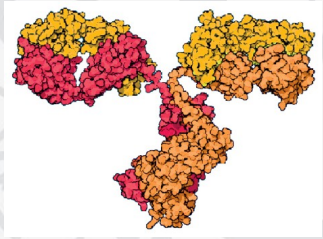
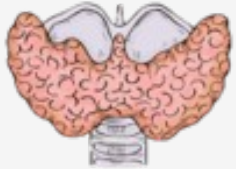


Thyroid Gland and Brain



Leonid P. Churilov

Supported by Russian Scientific Foundation Grant # 22-15-00113

Disclosure: I have nothing to disclose, just thanks to organizers

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Supported by Russian Scientific Foundation Grant # 22-15-00113

Thyroid regulation is essential for ontogenesis and functions of central nervous system:

The mechanisms of memory and learning are based on the plasticity of the CNS synaptic structures, provided, in particular, by the changes in the neuronal biosynthesis of RNA and proteins, which are involved in the potentiation of synaptic transmission. All these processes depend on thyroid hormones (TH).

1) TH increase the activity of **amino-acyl-t-RNA synthetases** in brain.

2) Production of **neurotrophic factors** depends on TH, and is impaired in the hippocampus,cerebellum and cortex in TH deficit.

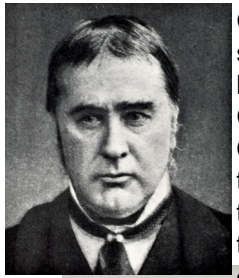
3) TH regulate **neuronal plasticity** associated with learning, and changes in the expression of their blood-carrier **transthyretin** serve as a characteristic correlate of **memory consolidation**.

4) The **reduction of neuronal networks** essential for maturation of brain as well as programmed cell death in the brain - both are based on TH-depending **apoptotic-like processes**.

5) TH via **activation of K+-Na+ -ATPase** may accelerate **bioelectric** processes in nervous system.

6) TH control the fate of **cerebral stem cells** & organogenesis of **cerebellum**

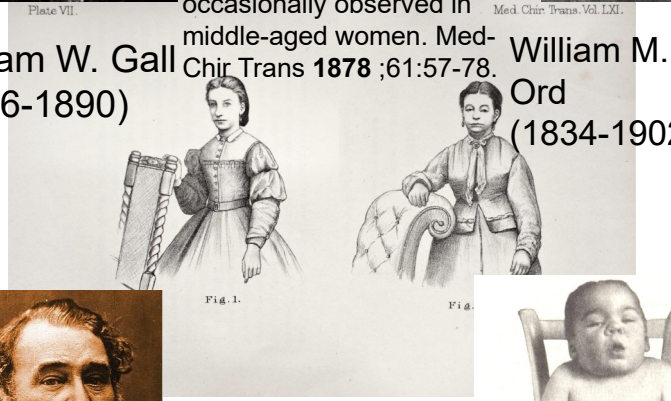
7) TH control **phagocyte behavior** and activity of cerebral **microglia**

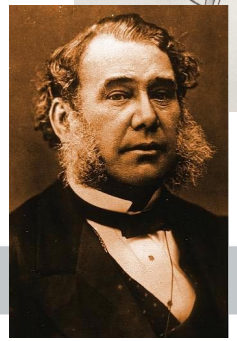


William W. Gall (1816-1890)

Gull WW, On a cretinoid state supervening in adult life in women, **1874,**Trans Clin Soc Lond 7:180-5;
Ord WM On myxoedema, a term proposed to be applied to an essential condition in the 'cretinoid' affection occasionally observed in middle-aged women. Med-Chir Trans **1878** ;61:57-78.

William M. Ord (1834-1902)





Charles H. Fagge (1838-1883)

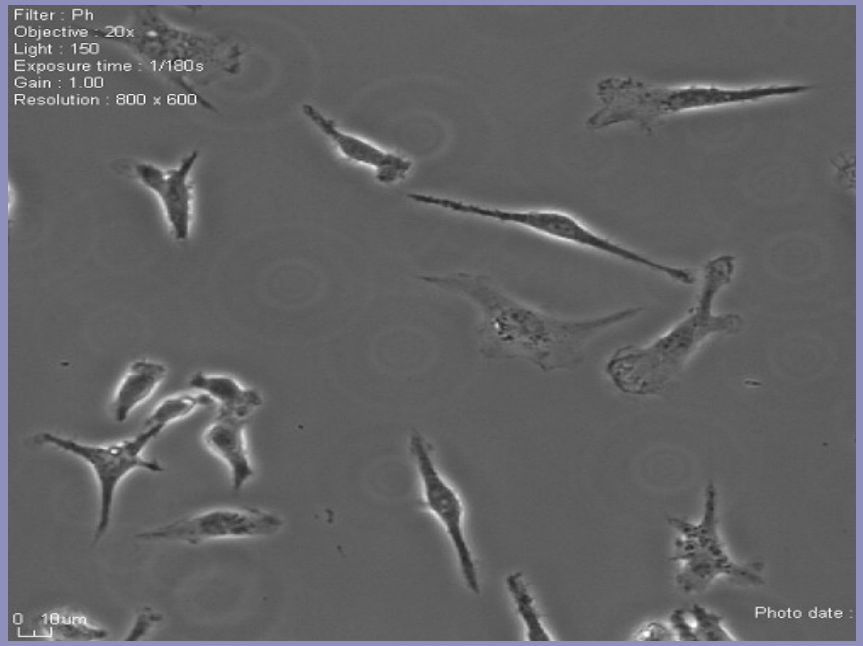
Fagge CH. On Sporadic Cretinism, occurring in England. Med Chir Trans. **1871;**54:155-170.1.

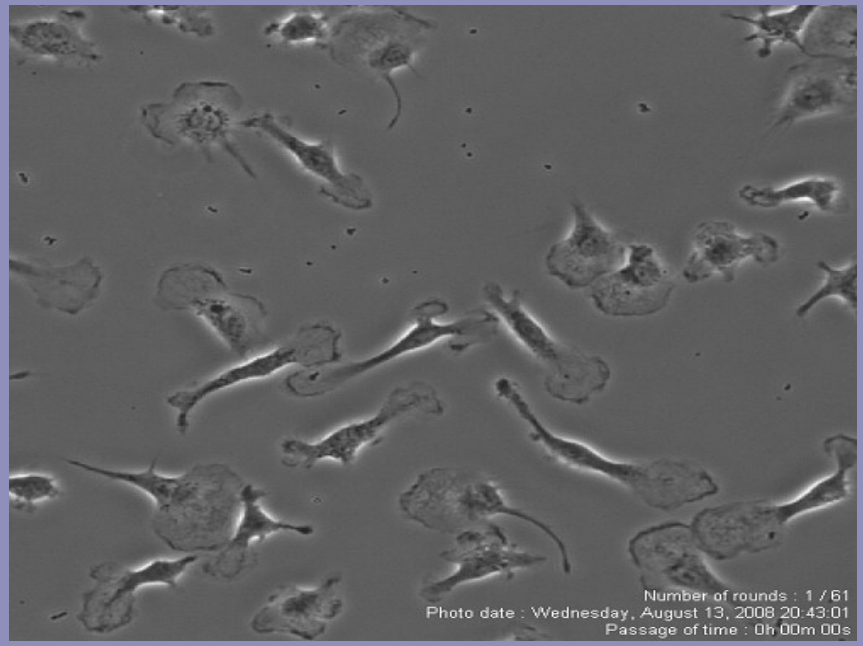
Рис. 111. Спорадический случай врождённого гипотиреоидного кретинизма (по У. Фальта, 1913).

Control

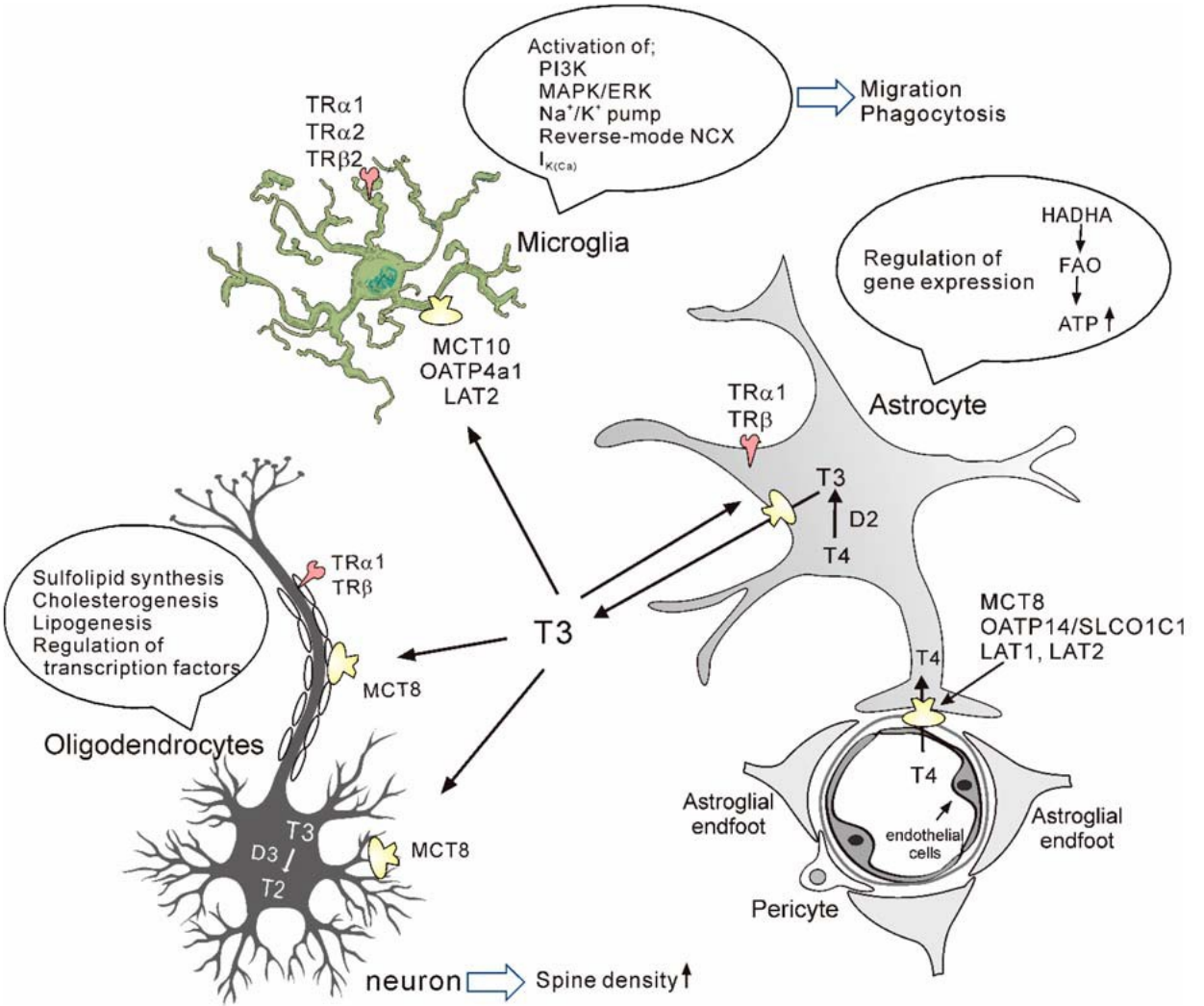
Influence of 10 mM concentration of T3 on microglial migration

[Mori Y, Tomonaga D, Kalashnikova A, Furuya F, Akimoto N, Ifuku M, Okuno Y, Beppu K, Fujita K, Katafuchi T, Shimura H, Churilov LP, Noda M. Effects of 3,3',5-triiodothyronine on microglial functions. Glia. 2015;63(5):906-20].



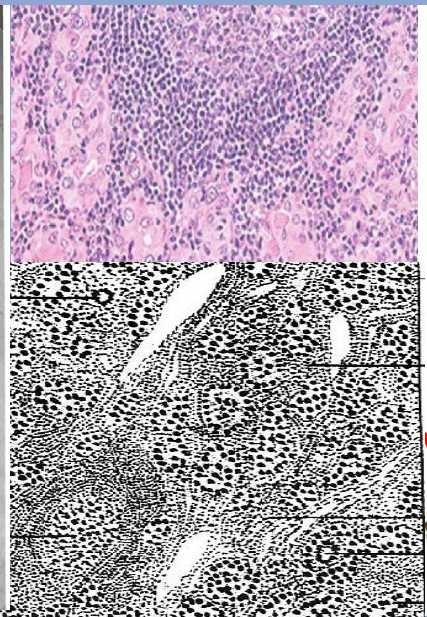


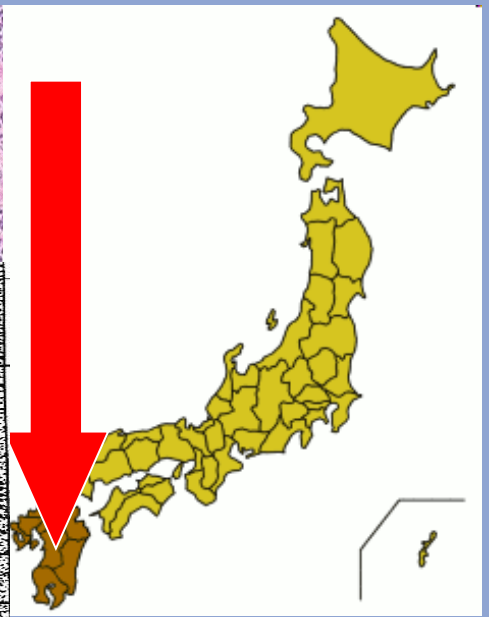
[DOI: http://dx.doi.org/10.2478/medu-2020-0001 • 3(1) • 2020]



In 1912Dr. Hakaru Hashimoto (1881-1934) has described chronic autoimmune thyroiditis (as "lymphomatous goiter") in Kyushu island, famous for its largest birthplaces of iodine-containing minerals. That was the first pathohistological description of human cell-mediated autoimmune disorder in the history of Pathology.

A surgeon described 4 female cases without any mention of some psychoneurological symptoms [Hashimoto H. Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa). Archiv für klinische Chirurgie (Berlin) 1912; 97:219—48]





During next 100 years the prevalence of Hashimoto disease dramatically i**ncreased worldwide** (maybe due to influence of **iodine and other adjuvant factors**) and it became globally **most frequent autoimmune disorder and most prevalent endocrinopathy,** a leading reason of hypothyroidism in wast areas with sufficient or excessive iodine supply.

Hashimoto's encephalopathy, birth of the term - Fathers:

MYXOEDEMATOUS MADNESS

BY

R. ASHER, M.D., M.R.C.P.

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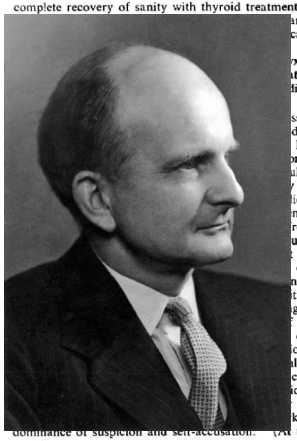
Myxoedema is one of the most important, one of the least known, and one of the most frequently missed causes of organic psychoses—important because it may respond so gratifyingly to treatment, little known because little has been written about it, often missed because the textbook description of myxoedema is not the rule but the exception.

Fourteen cases are here described, all of which had myxoedema and psychotic changes. In every one of them the diagnosis was confirmed beyond doubt. They all showed a psychosis amounting to complete "madness," ten being admitted to the mental observation wards under the Lunacy Act, one referred to the neurosurgeon for cerebral tumour, and three to general medical wards with other diagnoses. In nine of the cases there was a dramatic and complete recovery of sanity with thyroid treatment, in two



no special type.

Cases in the literature record a very wide variety of mental changes, and certainly in the series I have observed there has been no constant type of psychosis, though general confusion and disorientation with persecutory delusions and hallucinations, and occasional bouts of reckless violence, have been common. I have made the diagnosis on the myxoedematous appearance of the patient and not on the kind of mental symptoms. No physician would attempt to diagnose lobar pneumonia or typhoid by the delirium they may produce, and likewise in myxoedema it is the disease which is the characteristic feature, not its mental manifestations.

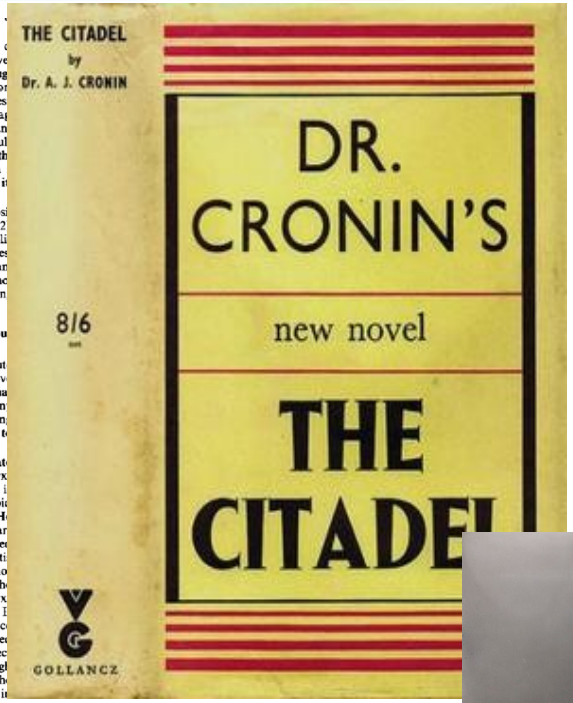
The fact that recorded cases of myxoedema psychosis have closely resembled paranoia (Case 1 and Stoll, 1932), schizophrenia (Zondek and Wolfsohn, 1944), melancholia (Buschan, 1896), or other orthodox psychoses does suggest that the common psychoses—schizophrenia, mania, melancholia, paranoia, and so on—may turn out to be not diagnoses in themselves, but manifestations of underlying organic disease.

Does the Response to Thyroid Prove the Myxoedematous Origin of the Psychosis?

First, if the case responds it is of course no absolute proof, because almost any type of psychosis can improve spontaneously. Nevertheless, when mental symptoms that have been present in a hypothyroid patient for many months clear dramatically within a few weeks of starting thyroid it is reasonably certain that they were due to myxoedema.

Secondly, if the mental changes persist after adequate thyroid treatment, does this mean they were not myxoedematous? As Ruhberg (1936) points out: "It is necessary to determine if they are secondary to thyroid insufficiency or merely a coincident concomitant." He states dogmatically: "If the mental symptoms are part of myxoedema, improvement and relief should be obtained by establishing a normal basal metabolic rate." Akelaitis (1936), discussing cases which showed physical but no mental improvement with thyroid, also concludes: "The psychosis was a coincidence and not part of the myxoedema." Such dogmatic assumptions are unjustified. It is generally agreed that metabolic changes can produce irreversible damage—for instance, the changes of prolonged hypoglycaemia or of pellagra may fail to respond respectively to glucose or to the vitamin B complex, although they were caused by deprivations of these. Again, the belated treatment of cretinism shows that the changes in the brain cannot be reversed by thyroid.

Dr. Leonard Simpson (personal communication) records such a case in which peculiar behaviour persisted after thyroid treatment and ultimately ended in psychosis. Hence



ENCEPHALOPATHY

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HASHIMOTO'S disease is usually a " silent " disorder, and has been regarded as a good example of autoimmune disease since the experimental work of Witebsky and Rose (1957) and the observations of Doniach and Roitt (1957) on serum antibodies in patients with thyroid disease. Yount (1960) wrote that it had no systemic manifestations. Becker et al. (1965) sought to link Hashimoto's disease with other possible autoimmune disorders; in a review of 153 patients with microscopically proven Hashimoto's disease at the Mayo Clinic between 1926 and 1960 (including 119 necropsies) 36 had associated diseases, such as rheumatoid arthritis, pernicious anæmia, myasthenia gravis, thrombocytopenic purpura, non-tuberculous Addison's disease, glomerulonephritis, polymyositis, idiopathic cirrhosis of the liver, disseminated lupus erythematosus, acute hæmolytic anæmia, scleroderma, and ulcerative colitis. 22 out of these 36 patients with Hashimoto's disease died from the associated disease, and Becker et al. concluded that " the association suggests that a basic generalised immunologic abnormality may exist in individuals with morphologic evidence of thyroiditis ".

In contrast, Masi et al. (1965) in a similar study at Johns Hopkins Hospital of 74 necropsies found no significant association of this kind; they pointed to various fallacies, including the tendency to report single unusual cases and Berkson's bias, whereby largely asymptomatic disorders like Hashimoto's disease were likely to be detected only when they were associated with a more prominent disease. In the following case-report, however, the apparent onset of Hashimoto's disease itself led to hospital investigations, and was followed within a few weeks by an extraordinary and puzzling neurological illness for over a year. No necropsy was performed. Myasthenia gravis (Daly, Finger and Sahay 1966) was found in association with Hashimoto's disease, and there was also seen Hashimoto's disease with ophthalmoplegia.

In 1953 a 40-year-old coachbuilder was found lying deeply unconscious at his place of work with a lacerated scalp; he was admitted to two hospitals, and made a slow but complete recovery. His cerebrospinal fluid contained 50 mg. protein per 100 ml., 6 cells per c.mm. (1 polymorph, 5 lymphocytes). It was thought to have had an unobserved head injury, and remained well for the next seven years.

In 1960, at the age of forty-eight years, while undergoing negative investigations for a slight hæmoptysis, he was seen to have become sleepy, podgy, and more sensitive to cold; he had a goitre and a puffy face, and the clinical diagnosis of Hashimoto's disease was confirmed by thyroid-antibody studies (table I), and thyroid biopsy. Thyroxin 0·2 mg. daily was begun in February, 1961, which was reduced to 0·1 mg. daily in March on account of restlessness and vomiting.

The Neurological Illness

On April 26, 1961, the patient complained of feeling unwell, and of dysæsthesia in the right arm and leg for a few hours. In May, 1961, he became tired and irritable, and on July 1 he was found struck down with sudden aphasia and right hemiplegia. He was conscious on admission to hospital but lapsed into tetraparetic coma with Cheyne-Stokes respiration. The pressure of his cerebrospinal fluid was normal, but the fluid contained 100 mg. protein per 100 ml. (table II). During the next week he recovered completely. In August there was another six stroke-like episodes in different areas of the brain (table III). From these episodes he would recover within a day without any residual abnormal neurological signs.

Bilateral carotid angiography on Sept. 3 was unremarkable but was followed by four days of confusion with bilateral extensor plantar responses.

On Oct. 10 the patient was readmitted because of sudden blindness in the right eye, which was followed by a sensory disturbance on the left side of the body. He had a left hem-

Richard A.J. Asher (1912-1969) **Archibald J. Cronin (1896-1981)**

Lord Walter Russell Brain (1895-1966)

ASHER R. Myxoedematous madness. Br Med J. **1949** Sep 10;2(4627):555-62.

Cronin A. J. The Citadel. Victor Gollancz Publishers: London a.e.; **1937.** p. 446.

Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet. **1966**; 2(7462):512-4.

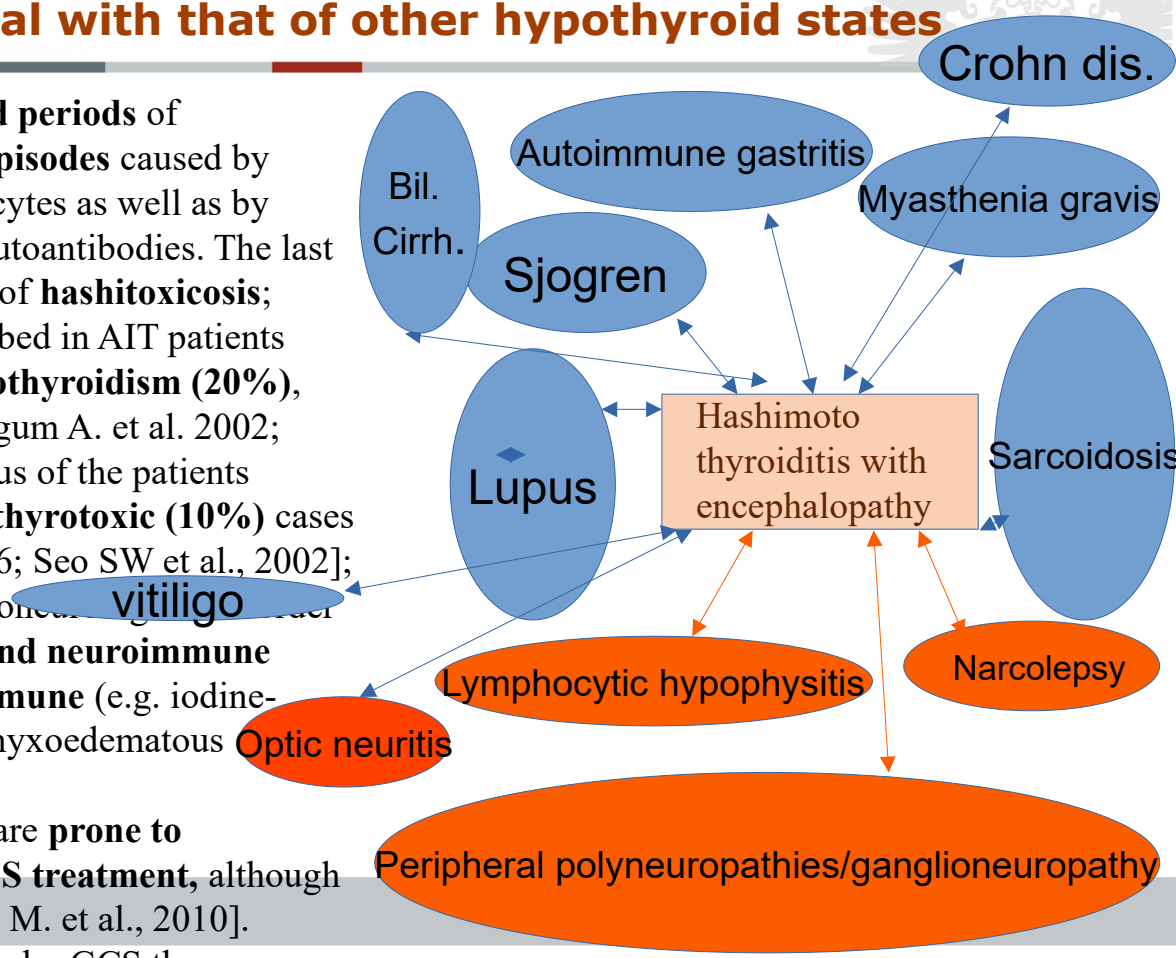
Brain manifestations of Hashimoto's disease are not merely results of hypothyroidism, with 2 patterns which may combine

Hypothyroidism (both in AIT and in non-autoimmune cases	**Hashimoto encephalopathy (in proven AIT with any thyroid status) — 2 patterns («stroke-like attacks» vs «indolent psychotic-like»**
tardiness and perseveration of thinking and speech, cognitive dysfunction down to organic dementia	cognitive dysfunction (36-100%)
memory loss, failure of skills and abilities	Psychosis symptoms (paranoid, visual hallucinations, mood disturbances, oneiroid syndrome, delirious manias and catatonia) – 25-36%
adynamia and akinesia	tremor (28-84%), seizures (52-66%), myoclonus (37-65%), epileptic status (12-20%)
asthenic syndrome	altered consciousness (26-85%), transient aphasia (73%-84%), focal deficit (27-67%). stroke-like episodes (18-31%).
depressive & phobic ideas	Cerebellar dysfunction: Gait disorder/ataxia (28-65%), muscle hypotonia, opsoclonus, dysmetria, and dysdiadochokinesia

Manifestations, comorbidities and treatment of Hashimoto thyroiditis with encephalopathy are not identical with that of other hypothyroid states

- The course of AIT may include **long euthyroid periods** of compensation and even display **hyperthyroid episodes** caused by thyroid hormone efflux from demolishing thyrocytes as well as by parallel effects of anti-TSH-receptor agonistic autoantibodies. The last phenomenon is inherent to quite common cases of **hashitoxicosis**;
- Picture of Hashimoto encephalopathy is described in AIT patients with **ANY** thyroid status, not only in **overt hypothyroidism (20%)**, but also in **slight or subclinical one (40%)** [Engum A. et al. 2002; Samuels MH, 2014] or in **euthyroid (30%)** status of the patients [Kirim S. et al., 2012].Even **hyperthyroid and thyrotoxic (10%)** cases of HE have been described [Barker R et al., 1996; Seo SW et al., 2002];
- Hashimoto thyroiditis and its associated psycho[illegible] are **comorbid with many other autoimmune and neuroimmune diseases**, which is **not the case for non-autoimmune** (e.g. iodine-deficient) cases of myxoedema and associated myxoedematous madness;

Major part of Hashimoto encephalopathy cases are **prone to immunodepressive and antiinflammatory GCS treatment,** although there are lot of **GCS-resistant cases** [Mijajlovic M. et al., 2010]. Hypothyroid mental disorder per se are incurable by GCS therapy.



EPIDEMIOLOGY AND AETIOLOGICAL FACTORS

The incidence of HE is estimated as **2.1/100 000** with **85% of female** cases, although several **most severe ones are described in males** [Ferrecci F. et al., 2004; Montanga M. et al., 2016].

Few possible risk factors mentioned in various case reports were the effects of **adjuvant-like** or **immunostimulating** agents of exogenous (**alpha-interferon, Epstein-Barr virus, checkpoint inhibitor Nivolumab, radio-Iodine, stem cell therapy**) [Arrojo M. et al., 2007; Bonnet U. et al., 2016; Hori T. et al., 2010; Maetani T et al 2019; Ruina et al. 2020; Vicent MG et al. 2019] or endogenous (**estrogens**) [Sella F. et al., 2002] origin.

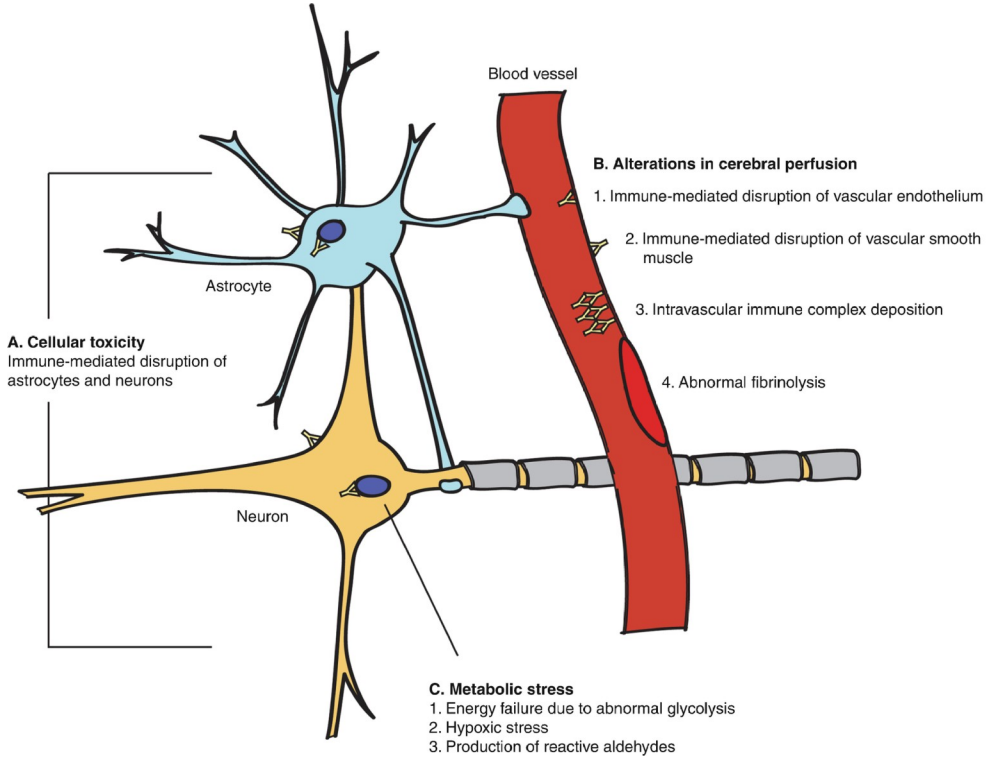
Lithium which produces TSH resistance of thyrocytes and alters reception of vasopressin was accused as one more provocation factor for HE [Nagamine M. et al., 2008].

The disease is most typical for female patients of **middle age (40-50 y. o.)**, although considerable number of **paediatric cases** was described (beginning from **14 months** old kid, but most of early cases observed during **menarche period of adolescent girls**), as well as few **geriatric** ones - up to a **86 y.o.** woman.

Pathogenesis of Hashimoto encephalopathy: 3 concepts prone to intermingle

Three major mechanisms were suspected in pathogenesis of HE:

- vasculitis-related (oldest, coined in pioneer paper by Lord Brain et al (1966);
- related to “toxic”/deregulatory influence of some hormones, excessively produced in response to hypothyroidism (Latinville D. et al., 1985);
- autoantibody-related (including those against not only thyroid, but also extrathyroid antigens) (Ghawche F. et al., 1992).



Chew S., Venna N. (2019) Hashimoto’s Encephalopathy. In: Cho T., Bhattacharyya S., Helfgott S. (eds) Neurorheumatology. Springer, Cham. https://doi.org/10.1007/978-3-030-16928-2_17

Pathogenesis of Hashimoto encephalopathy (HE): more detailed picture, the links not alternate, but intermingle:

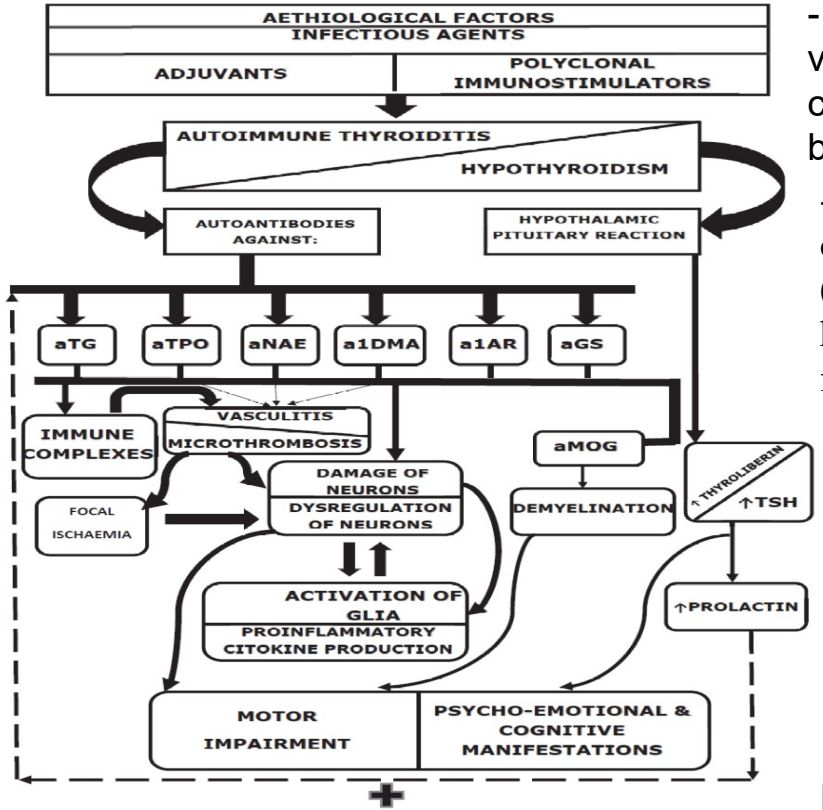
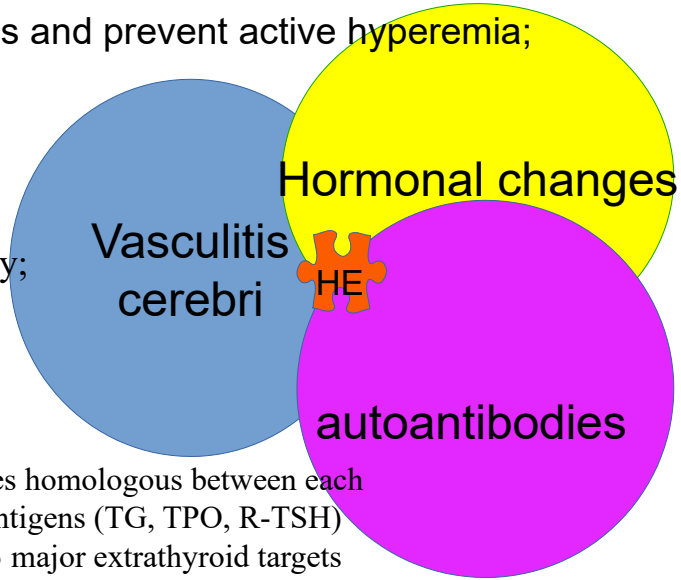


Fig. 1. Scheme of pathogenesis of HE. ABBREVIATIONS: a1AR — autoantibodies against 1-aldoreductase, a1DMA —autoantib against 1-dimethylarginase, aGS — anti-ganglioside autoantibodies, aMOG — autoantibodies against myelin-oligodend glycoprotein, aNAE — autoantibodies against N-terminal peptide of alfa-enolase, aTG — autoantibodies against thyroglo aTPO — autoantibodies against thyroid peroxidase, HE — Hashimoto's encephalopathy TSH — thyroid stimulating hormone.

- some autoantigens are shared by neurons, glia and vascular cells, thus vasculitis can be not only immune complex, but also cytotoxic. A1DMA autoantibodies block EDRF synthesis and prevent active hyperemia;

- some hormonal changes in AIT (hypothyroidism & hyperprolactinemia) facilitate autoimmunity;

- hormonal changes in AIT facilitate cerebral atherosclerosis and hypoperfusion

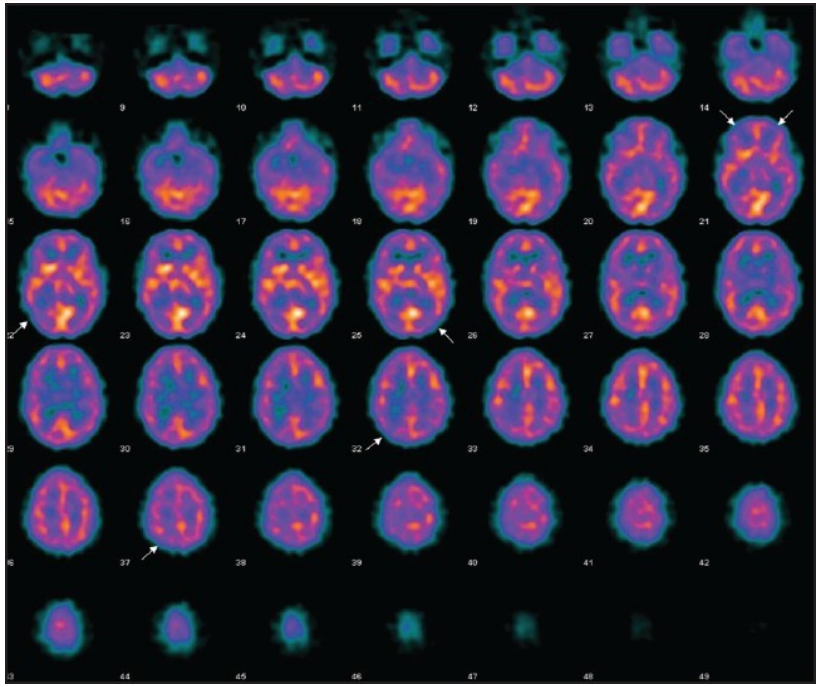


There are several peptides homologous between each of 3 major thyroid autoantigens (TG, TPO, R-TSH) and epitopes of each of 3 major extrathyroid targets (a1DMA, a1AR, disulphide-isomerase A3 [Benvenga et al., 2020]

Churilov LP, Sobolevskaia PA, Stroev YI. Thyroid gland and brain: Enigma of Hashimoto's encephalopathy. Best Pract Res Clin Endocrinol Metab. 2019 Dec;33(6):101364.

Pathogenesis of Hashimoto encephalopathy: vascular concept, *pro et contra:*

- presence of **hypoperfusion** zones on brain CT images in some of the cases, especially during mental exercise tests **lack of active functional hyperemia**);
- but many cases **do not show** that changes.
- thyroid is still out of scope of attention during post mortem autopsies, because AIT relation with potentially lethal metabolic syndrome so far is not comprehended by health care practitioners. But, few occasional autopsies of HE patients perished revealed **phlebitis** or **polyangiitis** through all the brain or at least in the brainstem. Small and medium-sized blood vessels or **perivascular spaces infiltrated with lymphocytes**, predominantly of T-subsets. [Tsai SL e.a., 2011; Duffey P. e.a., 2003].



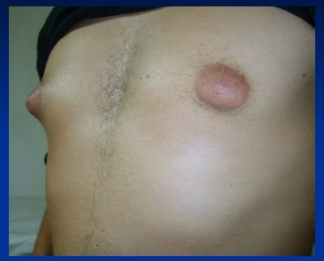
Transaxial brain single-photon emission computed tomography images with irregular and patchy decreased cortical tracer uptake of both hemispheres (arrows) [from:**Grande ML, et al.** Brain hypoperfusion on Tc-99m-ethylene dicysteine diethyl ester single-photon emission computed tomography in Hashimoto's encephalopathy. Indian J Nucl Med. **2013**;28(2):

Pathogenesis: Hormone-related concept is still alive

Hashimoto thyroiditis always causes compensatory increase in **thyroliberin** and TSH. Initial dyshormonal concept related HE to t**he ability of thyroliberin induce tremor, seizures, epileptic activity and alter cerebellar degeneration** which all may occur in HE. High **effectiveness of L-thyroxine treatment without GCS** was also interpreted as a witness for this concept. Ishii K. et al. (1995) **experimentally reproduced exacerbation of HE with typical motor disorders in a volunteer patient by injection of thyroliberin** Now this theory is semi-forgotten, although it has important new facet. **Thyroliberin is also potent prolactoliberin.** That's why AIT and HE commonly proceeds with hyperprolactinemia. Prolactin is well known autocrine, paracrine and endocrine stimulator of autoimmunity. This may create a vicious circle in HE pathogenesis. High hyperprolactinemia is psychopathogenic *per se* and causing infertility may **secondarily alter mental health** of a patient. Anti-psychotic **neuroleptics** which cause hyperprolactinemia in many cases **aggravate** HE

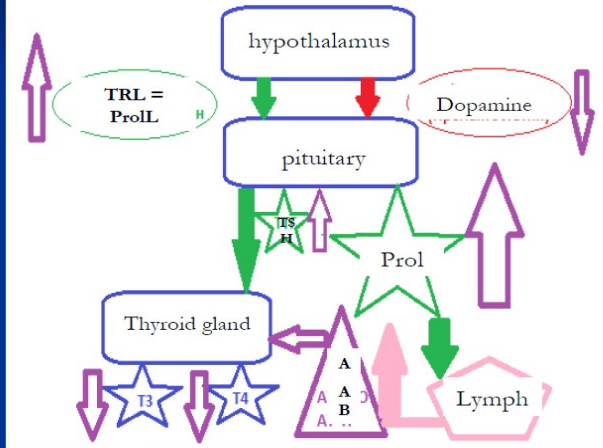
Hyperprolactinemia in Hashimoto thyroiditis: effect of viscious circle with alteration of reproductive potential and psychics

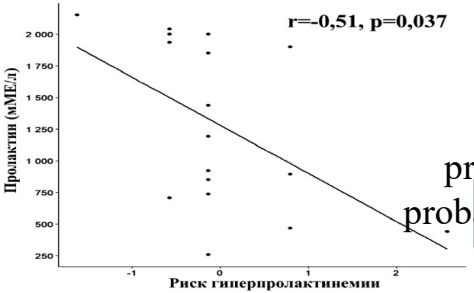
The consequences include not only disorder of reproduction, but also mood disorders and secondary promotion of autoimmunity



Fact of prolactoliberin and thyroliberin effects overlap was proven by P.J. Sneider et al. relatively long ago (1973)

Prolactin is systemic and paracrine stimulator of autoallergy [Orbacha H., Schoenfeld Y., 2007]. Hyperprolactinemia is typical for AIT because of progressing hypothyroidism and prolactoliberin-like effect of compensatory produced thyroliberin





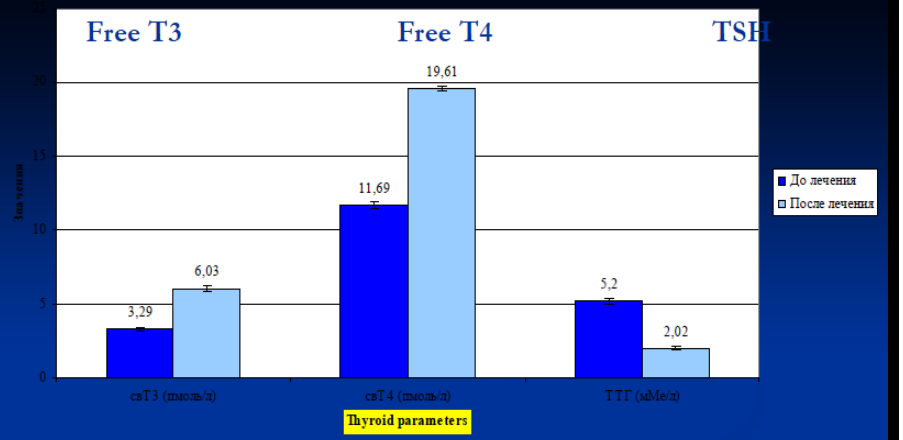
In our study of HE patients treated with neuroleptics the correlation between nominal risk of drug-related hyperprolactinemia and real level of prolactin was strong **BUT INVERSE**. It probably was not iatrogenic but inherent to HE pathogenesis

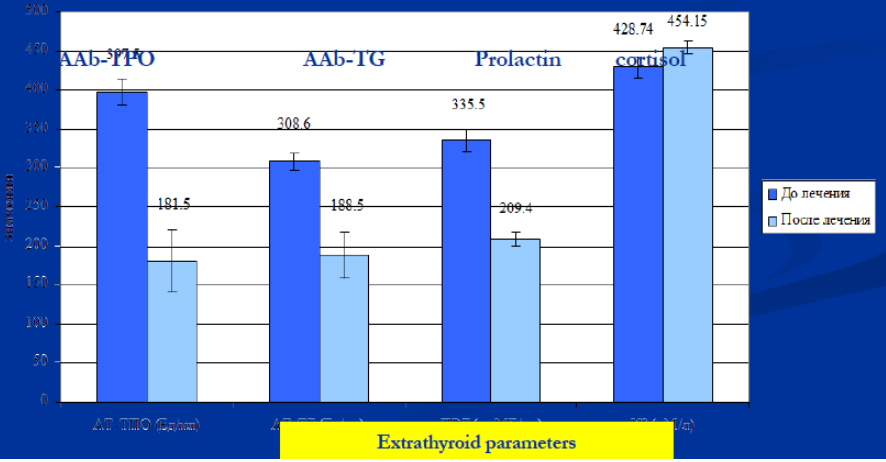
Hypothyroidism in AIT+HE may act not only as endocrine factor, but also *via* immunomodulation

WHAT IS THE EFFECT OF THYROXINE IN COMPLICATED AIT & HOW IT WORKS?

EFFECT IS NOT ONLY SUBSTITUTIVE, BUT ALSO IMMUNE MODULATING,

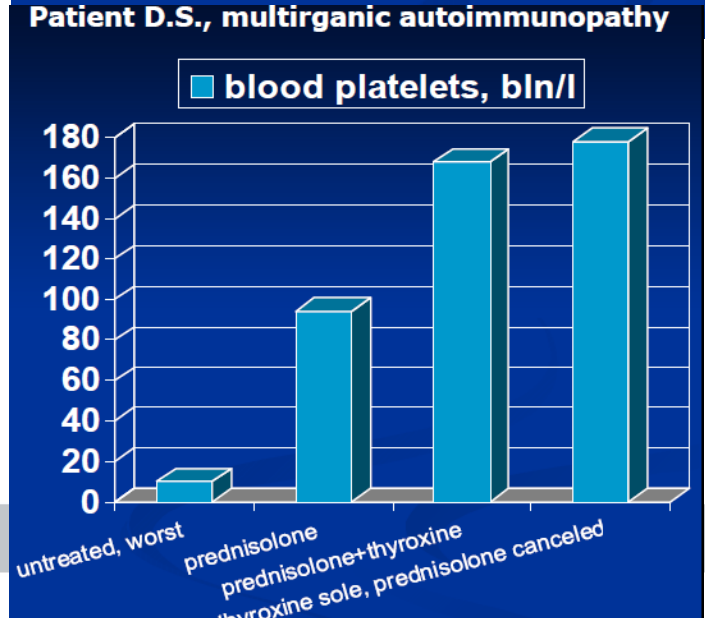
IT DOES NOT INVOLVE DIRECT CORTISOL IMMUNE DEPRESSION, BUT INVOLVES DECREASE OF PROLACTIN





Hypothesis: hypothyroidism delays apoptosis of autoreactive lymphoid clones, thus self-aggravating AIT (vicious circle). Treatment with thyroid hormones decrease anti-platelet antibodies and increase platelets WITHOUT GENERAL IMMUNOSUPRESSION. Thyroxine effectiveness was better than prednisolone

Mihara S. et al. Effects of thyroid hormones on apoptotic cell death of human lymphocytes // J. Clin. Endocrinol. Metab. – 1999. – Vol. 84. – P. 1378-



Pathogenesis of HE: just anti-TPO or set of anti-thyroid or even extrathyroid minor AAB specificities?

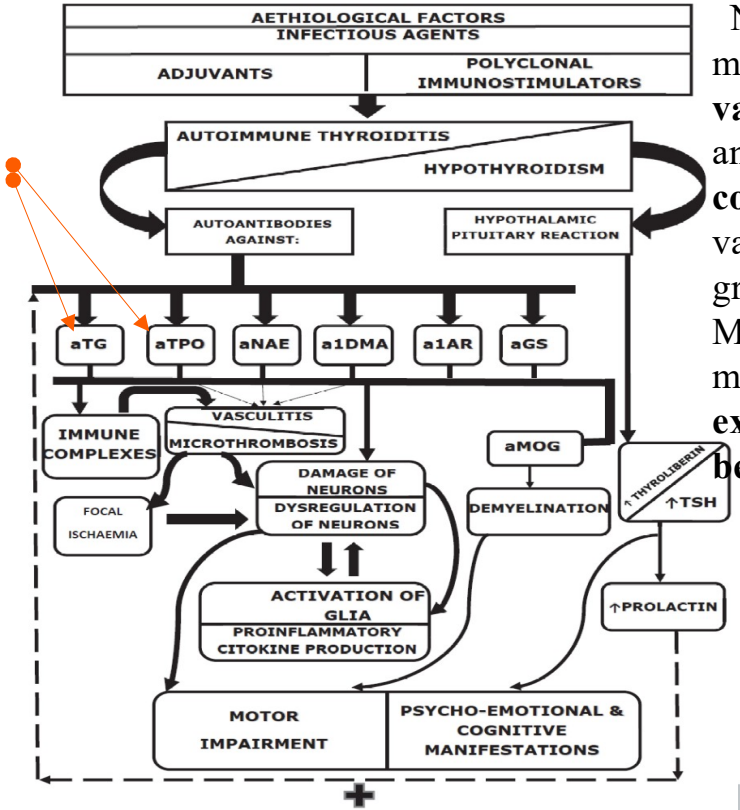
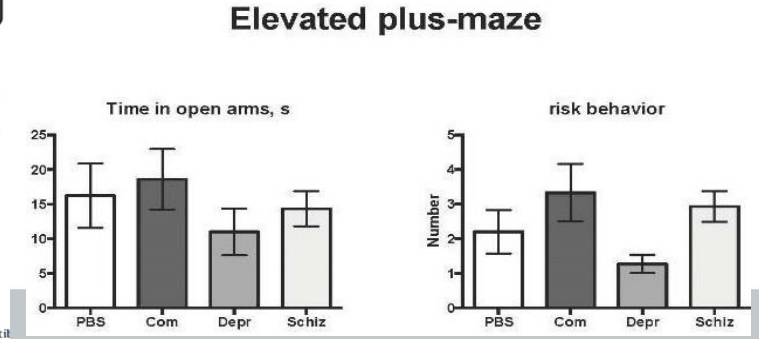
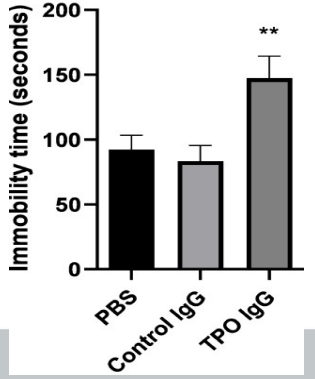


Fig. 1. Scheme of pathogenesis of HE. ABBREVIATIONS: a1AR – autoantibodies against 1-aldoreductase, a1DMA –autoantil against 1-dimethylarginase, aGS – anti-ganglioside autoantibodies, aMOG – autoantibodies against myelin-oligodend glycoprotein, aNAE – autoantibodies against N-terminal peptide of alfa-enolase, aTG – autoantibodies against thyroglc aTPO – autoantibodies against thyroid peroxidase, HE – Hashimoto's encephalopathy TSH – thyroid stimulating hormone.

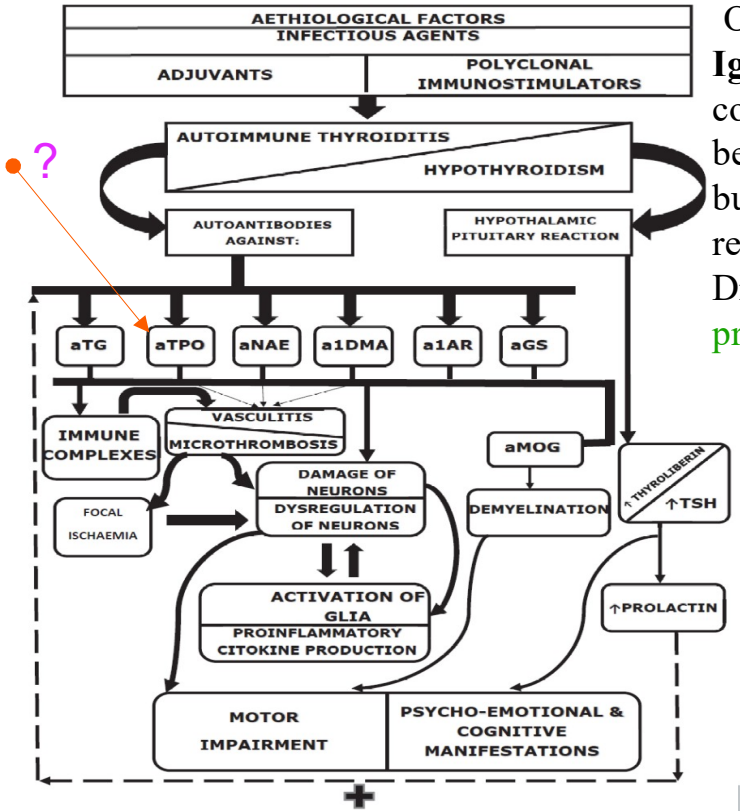
Neither TPO, nor TG, nor TSH-R – are **NOT unique** organe-specific markers. **Anti-thyroglobulin** autoantibodies recognize antigens of **cerebral vasculature**, **anti-TSH-receptor** autoantibodies bind to **cortical neurons,** and **aTPO** localize on **astroglial cells of cerebellum and on cerebral cortex**. TPO also has **homology with endothelial peroxidase** of cerebral vasculature and there was described a combined case of Wegener's granulomatosis and Hashimoto encephalopathy [Crisanti P. et al. 2001; Moodley K. et al., 2011; Blanchin S. et al., 2008]. Anti-TPO and anti-TG may affect **cerebral glucose** metabolism [Pilhatsch M. et al. 2014]. Thus, **extrathyroid symptoms of Hashimoto's disease which involve CNS can be mediated** ***via*** **anti-thyroid autoantibodies.**





Behavioral abnormalities induced by specific IgG in mice.(Shoenfeld. Drori, Shavit-Stein, Sobolevskaia, Churilov et al., unpublished data, in press)

Pathogenesis of HE: just anti-TPO or set of anti-thyroid or even extrathyroid minor AAB specificities?



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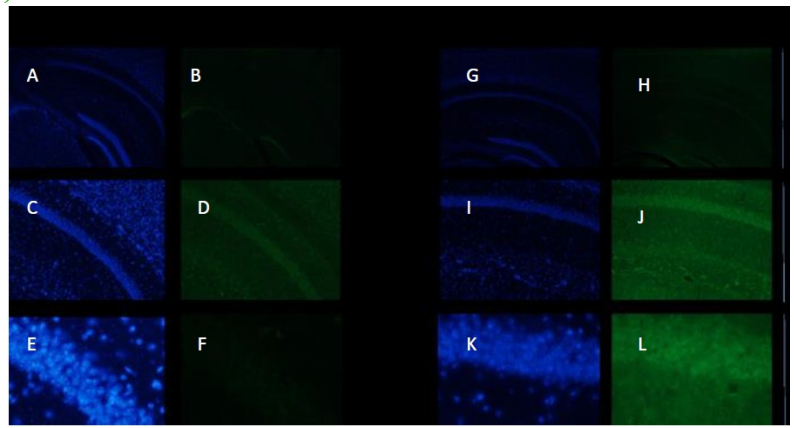
Our attempts to create a **mice model of HE** with **polyclonal anti-TPO rich IgG from HE patients** were just relatively successful. Polyclonal mixture contained AAB of minor specificities also, not exclusively anti-TPO. Also, behavioral abnormalities were clear after intrathecal intracerebral injection, but after intracysternal precise injection under stereotaxic control they were reproduced just partially and with borderline statistical reliability (Shoenfeld. Drori, Shavit-Stein, Sobolevskaia, Churilov et al., unpublished data, in press).

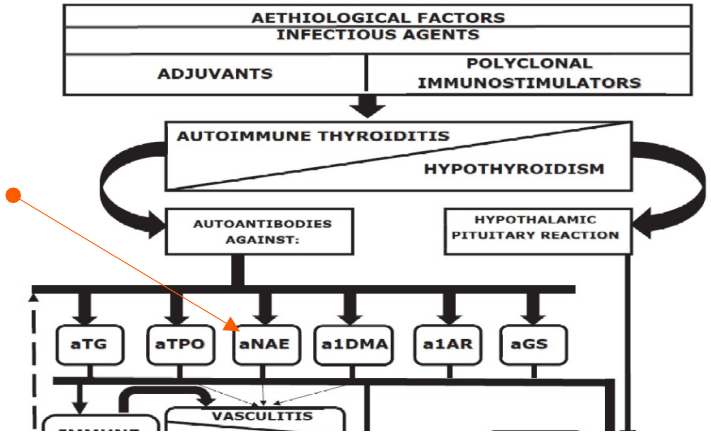


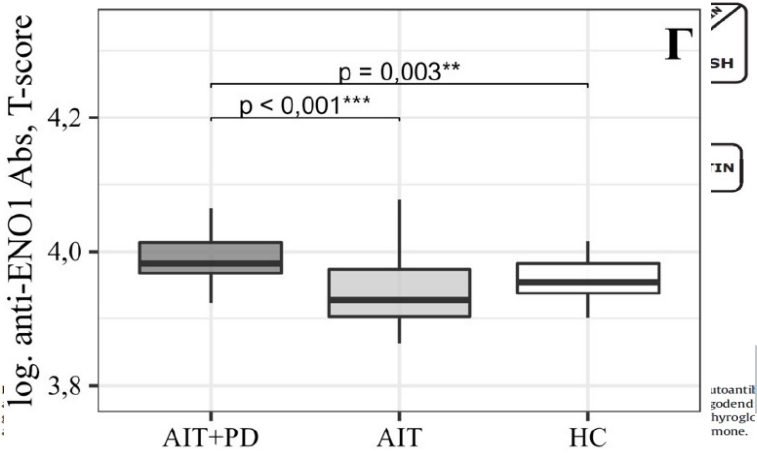
Immunofluorescent staining of normal mouse brain sections after intratechal injection of commercial control IgG (A-F) or anti-TPO IgG (G-L). Dentate gyrus and the CA1 layer of hippocampus (G, H).

At the x10 magnification, higher intensity staining of CA1 region by anti TPO (I, J) compared to control (C, D). x40 magnification shows a specific binding of anti-TPO to pyramidal cells soma at CA1 region (K ,L).

Pathogenesis of HE: minor AAB specificities - alpha-enolase

Strong objections from: Mattozzi S, et al. Neurology. 2020; 94(2):e217-e224. doi: 10.1212/WNL.0000000000008785.



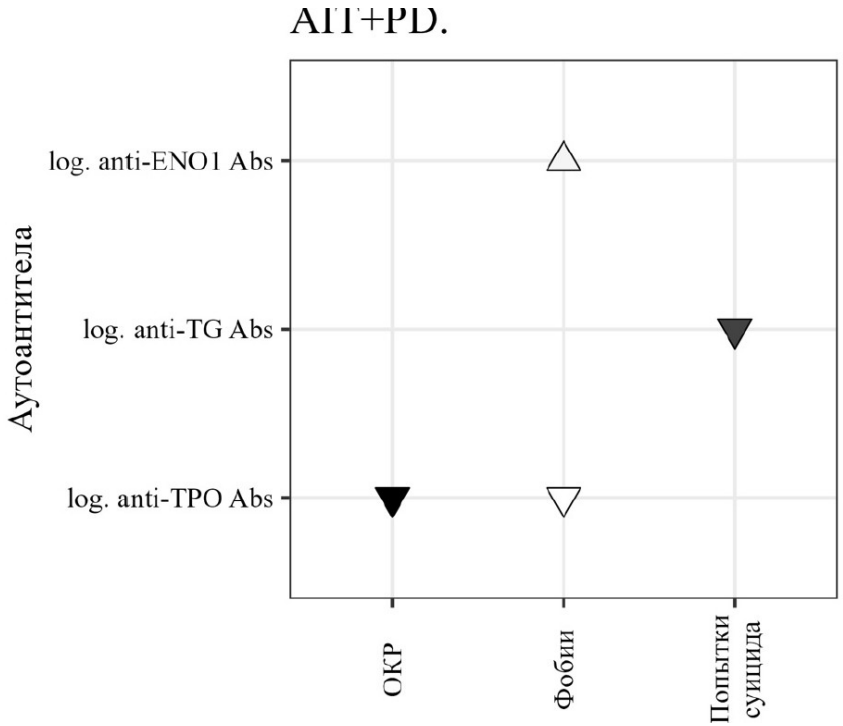


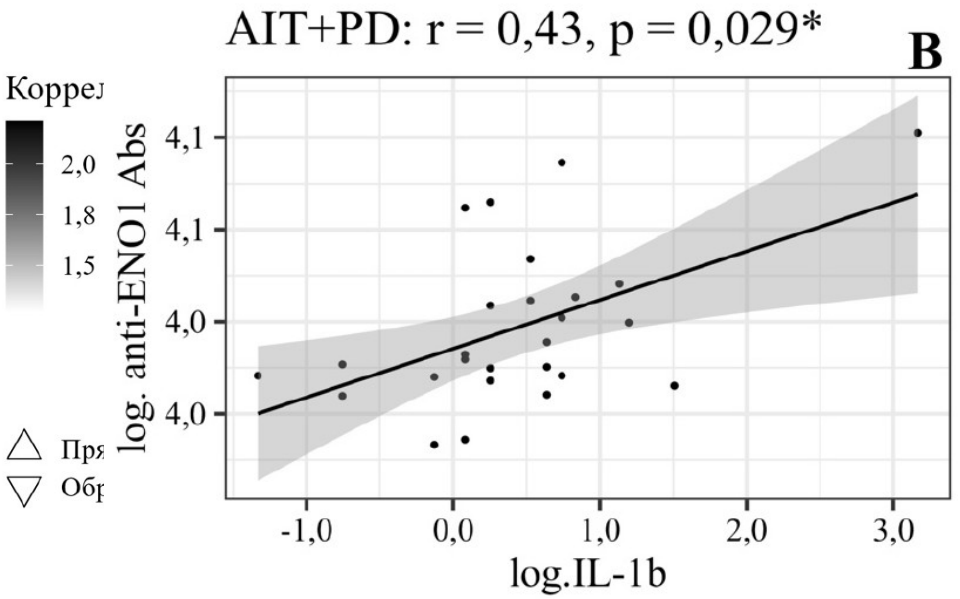
Autoantibodies towards **N-terminal of alpha-enolase (aNAE)** revealed in many cases of HE (60-83% by ELISA & proteome analysis [Ochi H, et al, 2002; Fujii A, et al. 2005, Yoneda M. et al., 2007]. Brain magnetic resonance imaging (MRI) revealed in HE patients positive for aNAE diffuse non-specific white matter abnormalities and multiple small subcortical limbic lesions **worsened in relapses and improved after recovery** [Matsunaga W. et al., 2019].

Alpha-enolase is targeted in many other autoimmunopathies. **Cross-reactivity** exists between peptides of **human** enzyme and enolases from **Candida & Streptococci**,which already was shown to be essential for rheumatiod arthritis. Enzyme binds **plasminogen,** hence idiotype-antiidiotypic interactions with aNAE may **alter coagulation**, like in APS.

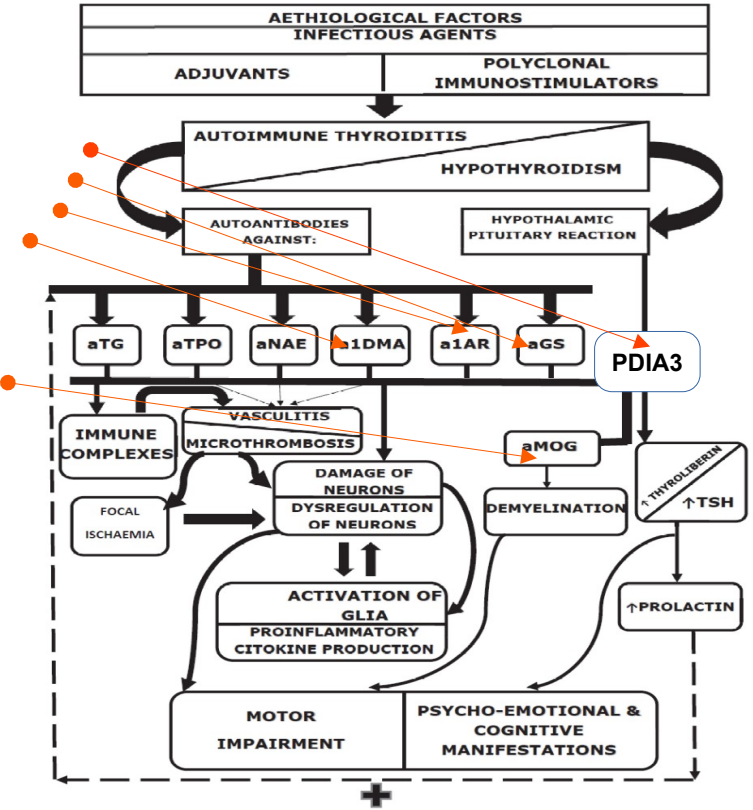
It is expressed in **cerebral vessels** and **embryonic neurons.** It has a **close homologue gamma-enolase** expressed in neurons and paraneurons, but also in pituitary and **C-cells of thyroid**, as well as in thyroid and other cancer cells. Hence aNAE may elicit as **paraneoplastic** one. **AAB against alpha- and gamma-enolases cross-react with targets in autoimmune hypophysitis** (O'Dwyer DT et al., 2002]. Oncocytes or **Hürthle-Askanazy cells** (with dysplastic mitochondria) are abundant in Hashimoto thyroiditis and co-express plenty of gamma-enolase and TPO.

Anti-aNE autoantibodies correlate positively with some manifestations of HE as well as with levels of some pro-inflammatory cytokines





Pathogenesis of HE: roles of other minor AAB specificities:



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AAB to **dimethylargininase-1 (a1DMA)** were revealed in sera and CSF of some HE patients (Oide T. et al. 2004; Gini B. et al., 2008; Verhelst H. et al., 2011]. Dimethylarginase-1 is involved in **production of endothelial-derived relaxing factor** or nitric oxide, thus establishing important SMC relax signal for functional arterial hyperemia in acting portions of brain. Its failure **may be related to regional hypoperfusion on exercises,** earlier noticed in HE.

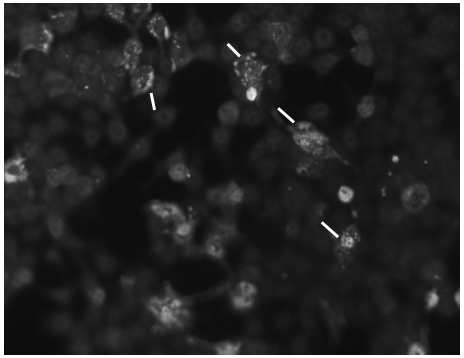
AAB to **aldehydereductase 1 (a1AR)** also revealed both in sera and CSF in some cases of HE (Gini B. et al., 2008, Verhelst et al., 2011). **1AR- is a cytoprotective enzyme for brain in hypoxic and free radical necrobiosis.** Its failure may cause loss of neuronal viability. AAB to **disulphide-isomerase A3 (PDIA3),** an enzyme controlling cancer cell proliferation and HLA proteins folding may alter these processes and be elicited as paraneoplastic ones [Yang W. et al 2020]

AAB to **non-enzymatic** targets - (**myelin-oligodendrocyte glycoprotein (aMOG)** and **gangliosides (aGS)** sometimes occur in HE [Chen KA, et al. 2017; Mussig K. et al. 2008]. Former may take part in **demyelination process** in foci of encephalopathy, later **may hit the ganglioside moieties of many cAMP-associated hormonal and neurotransmitter receptors** (like, TSH). Their level **correlates with cognitive impairment** in HE.

"Practitioner is interested mostly in differences between diseases, but pathologist – mostly in their similarities" (Hans Selye)

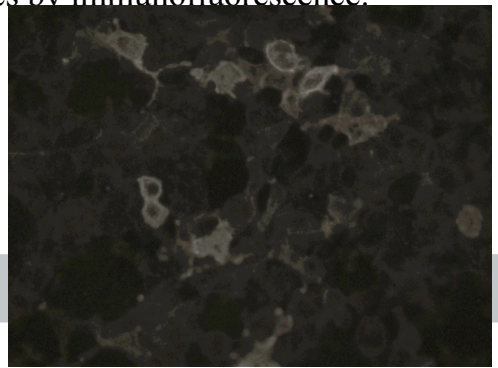
The HE displays a considerable **overlap** with a family of **autoimmune encephalitides** (both p**araneoplastic and non-paraneoplastic** ones) caused by **anti-receptor and anti-ion channel autoantibodies.** Among the long list of them, HE is especially close to different varieties of **anti-NMDAR, anti-GABA and anti-AMPAR disorders**, sharing with them depressive and hallucinatory symptoms and appropriate autoantibodies (towards NR1, NR2b, AMPAR2, GABAAbR etc). Sometimes the differentiation between HE and autoimmune paraneoplastic encephalitides is additionally hardened because **focal cerebral lymphoid infiltration** in HE may produce on MRI pictures **similar to that of tumors**. Among over **500 cases of HE** described in medical literature so far there are many which represent either **masks of above mentiioned encephalitides**, or **authentic subtypes of limbic encephalitides** caused by above-mentioned autoantibodies (e.g. aNAE). *Our experience of **24 cases of AIT+psychoses** (in other words – HE) also contains 2 similar cases. One is a case of a 36-year-old woman who was diagnosed with schizophrenia. The patient had high titers of **anti-TPO** and was positive for autoantibodies towards **glutamate receptors (type NMDA).** Another one is 56 y.o. women with **AIT+bipolar affective disorder** positive for both **anti-TPO & anti-GABA-B receptor** antibodies.*
*Both cases by **Sobolevskaia PA et al.** are in press in Dubai Med. J., 2021, 3(7) and in Psychiatria Danubina, 2021, **not yet published.***

Case 1



Top: Positive stain for **anti-glutamate receptor antibodies (NMDAR type)** by immunofluorescence (arrows).
Bottom: Positive stain for **GABA-B receptor** antibodies by immunofluorescence.

Case 2



Conclusions

In spite of almost 200 years of scientists' efforts, still not all facets of thyroid/brain/immunity interactions are clear, and HE remains one of the enigmatic phenomena, both for Thyroidology and Psychiatry.

The pathogenesis of HE may include direct action of various autoantibodies on target cells within CNS, like it occurs in autoimmune encephalitides, but also depends on indirect links, mediated via secondary cytokine production and/or metabolic effects of autoimmunity and changes brain perfusion and function of thyrostate servomechanisms.

Anyway, HE is a bright illustration of the statement that behavior is constructed not only by CNS, but by immuno-neuroendocrine trinity as a whole.

It is not just a result of efforts from parents, teachers, care-takers, mass media and impact of God's Will. It is integral result of individual genome functioning carried out *via* metabolism and its immuno-neuroendocrine regulation.

Hence all mental disorders are equally somatic ones.

Thank you for attention!
All the details and references available here:

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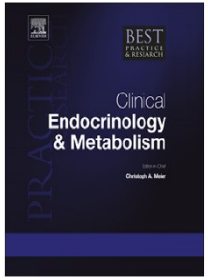

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Thyroid gland and brain: Enigma of Hashimoto's encephalopathy

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ARTICLE INFO

The versatile clinical manifestations of the Hashimoto's chronic