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Autoimmune manifestations of the post-COVID-19 condition

Varvara Ryabkova[1], Anna Bregovskaya[2], Lidiia Soprun[1,3], Natalia Gavrilova[1,3,4*], Leonid P. Churilov[1,4]

[1]St. Petersburg State University, Laboratory of the Mosaic of Autoimmunity, 199034, Universitetskaya Emb., 7-9-11, St. Petersburg, Russia
[2]Almazov National Medical Research Centre, 197341, Akkuratova str., 2, St. Petersburg, Russia
[3]St. Petersburg State University Hospital, 190103, Fontanka river Emb., 154, St. Petersburg, Russia
[4]St. Petersburg Research Institute of Phthisiopulmonology, 191036, Ligovskii pr., 2-4, St. Petersburg, Russia

***Correspondence to**
Natalia Gavrilova, Email: fromrussiawithlove_nb@mail.ru, n.y.gavrilova@spbu.ru

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Abstract

In 2020, the world suffered an epidemic of a new coronavirus infection, after which it became obvious that the consequences of this disease persist for a long time after the recovery, perhaps, for several months. This complication was called post-COVID-19 syndrome and was recognized by the World Health Organization, which was reflected in the Delphi Consensus on October 6, 2021. The clinical characteristics of this disease include a significant number of immunological manifestations, including fever, arthralgia, myalgia, flu-like symptoms, as well as autoimmune diseases manifestation. These symptoms may allude the autoimmune genesis of the COVID-19 complications. This mini-review summarizes the current understanding of the systemic manifestations of COVID-19 and the possible role of impaired immune function in the pathogenesis of post-COVID-19 syndrome.

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Introduction

There is an accumulating body of evidence regarding the late-onset complications of COVID-19, of which autoimmune manifestations have attracted remarkable attention from the first months of the pandemic. Viral infections are well reported to be associated with, or exacerbate, autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus (1). Both bystander activation and to a greater degree, molecular mimicry which are the main mechanisms of viral induced autoimmunity have been proposed to occur in COVID-19 patients. Among the recent reports on the autoimmune complications of COVID-19 Guillain-Barré syndrome, immune thrombocytopenic purpura and Kawasaki disease constituted the majority (2). However, the most common autoimmune complication of the novel coronavirus infection may be different. The combination of persistent symptoms following COVID-19 has been recently recognized by the World Health Organization (WHO), which released the first clinical case definition of "post-COVID-19 condition" on October 6, 2021 (3). Although this condition does not meet the criteria of any known autoimmune disease, it could mimic rheumatic disease due to shared clinical features, laboratory and imaging findings (4). It should be also noticed that "inflammatory/hyperinflammatory state" and "immune dysregulation/autoimmune" rank first among the proposed mechanisms of post-COVID-19 condition according to the results of the Webinar held on this issue by WHO on June 15, 2021 (5).

Key point

Post-COVID syndrome is an important healthcare issue, which may have an autoimmune nature. Clinicians should be aware of autoimmune manifestations of post-COVID-19 condition and further studies both observa-tional and experimental are required to establish the role of autoimmune/immune-mediated mechanisms its pathogenesis.

The first reports of a multisystem inflammatory syndrome in children (MIS-C) related to COVID-19, which appeared in late April 2020 provided one of the important clues to the association of autoimmunity with COVID-19 (2). SSince MIS-C develops 3–6 weeks after contracting COVID-19, one could suggest that MIS-C is an infection-associated autoimmune disease. The findings of a recent study conducted by Porritt et al (6) pointed to an autoimmune phenotype in MIS-C characterized by dysregulated B cell responses, autoantibody production and

complement- and myeloid cell–mediated inflammation. Chen et al (7) in their perspective article focused on the imbalanced Th17/Treg regulation for explanations of the same and different manifestations among Kawasaki disease and MIS-C. They postulated two phases during the development of both Kawasaki disease and MIS-C syndrome as the early Th17 reaction and late Treg resolution stage which have different immunopathogenic processes with individual biomarkers and require different immunotherapies.

Regarding systemic autoimmune diseases, a similar incidence of systemic rheumatoid diseases post positive SARS-CoV-2 PCR (polymerase chain reaction) results and among the PCR negative comparators have been reported (8). However, further research is required both regarding the incidence of new-onset systemic rheumatic autoimmune diseases and clinical course of previously diagnosed ones after COVID-19. This type of studies is emerging. Mazurov et al (9) analyzed the clinical course of immunoinflammatory rheumatic diseases in 324 patients who survive COVID-19. Transformation of undifferentiated arthritis into various rheumatic diseases was observed in 49% of patients (more often into early rheumatoid arthritis). Furthermore, exacerbation of the underlying disease was reported in 83.4% of patients with an advanced stage of rheumatoid arthritis.

Patients with severe COVID-19 have increased levels of autoantibodies, including those that have known associations with autoimmune diseases. However, no consensus on clinical significance of these autoantibodies was existed (1). In particular, there is a robust debate on the role of antiphospholipid autoantibodies in COVID-19-associated thrombosis. The recent systemic review on this issue indicates that simple descriptive data are not sufficient to clearly determine antiphospholipid autoantibodies involvement in COVID-19 infection (10). Further follow-up studies to research the persistence of these antibodies over time as well as experimental studies directly investigating the pathogenic role of antiphospholipid autoantibodies are important. The issue will be to determine if they participate directly in thrombosis, or if their presence is only an additional feature of the major infectious pro-inflammatory state of the disease. It has been suggested that autoantibodies presence following COVID-19 is a reactive phenomenon similar to other infectious diseases as these autoantibodies are short-lived and fade away eventually in COVID-19 patients, therefore the presence of strongly positive autoantibody would favor the diagnosis of systemic rheumatic autoimmune diseases rather than post-COVID-19 condition. At the same time, it has been shown that latent poly-autoimmunity characterized by increased levels of different autoantibodies and proinflammatory cytokines and observed during the acute phase of COVID-19, persisted in patients with post-COVID-19 condition 7-11 months after acute COVID-19 (11). Meanwhile, it was observed that transient immunosuppression or immunodeficiency, that is followed by an acute reactivation of the immune system may lead to the development of autoimmune reactions (12). This hypothesis of inappropriate immune reconstitution in genetically susceptible individuals with the loss of self-tolerance was proposed (12) and could explain the occurrence of post-COVID-19 condition in immunocompetent patients who are not appeared to suffer from the prolonged immunosuppression after acute COVID-19. Finally, cross-reactivity of the antibodies against SARS-COV-2 as a possible mechanism of autoimmunity following COVD-19 is not just a hypothesis.

To summarize, in a similar manner to several viruses, such as Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, SARS-CoV-2 may have the ability to contribute to autoimmunity (13). Numerous records demonstrate the likelihood of COVID-19 patients to develop over 15 separate types of autoantibodies along with above ten distinct autoimmune diseases (13). A recently recognized post-COVID-19 condition shares a lot of clinical manifestations and also some laboratory and imaging findings with autoimmune rheumatic diseases, which suggest common hyperinflammatory/autoimmune mechanisms in their pathogenesis. Considering the earlier experience of the delay between the surge in the number of MIS-C or Kawasaki-like conditions and the spread peaks of COVID-19, a time gap is expectable between the COVID-19 pandemic and autoimmune presentations. Long latency period of sub-clinical autoimmunity with the presence of specific autoantibodies corresponds to the multistep concept of the development of autoimmune disorders, which might explain the onset of the clinical autoimmune disease sometimes years after the exposure to the potential trigger (14). Numerous studies have reported the presence of various specific autoantibodies that precede the clinical onset of different autoimmune diseases (e.g. primary biliary cholangitis, rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, autoimmune thyroid diseases, multiple sclerosis, celiac disease, autoimmune Addison's disease, systemic sclerosis and Sjogren's syndrome) sometimes by several years (14). Immune-related adverse events of immune checkpoint inhibitors therapy, which may develop as early as after the first dose or as late as more than 18 months after the start of the immunotherapy and even months after the immunotherapy has been discontinued, could be a good example of the stochastic nature of autoimmune reactions (14). Clinicians should be aware of autoimmune manifestations of post-COVID-19 condition and further studies both observational and experimental are required to establish the role of autoimmune/immune-mediated mechanisms in its pathogenesis.

Authors' contribution

VR and NG were the principal investigators of the study. AB and LS were included in preparing the concept and design. LP revisited

the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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