УДК 578.834.1:616-092+616-06

СИНДРОМ ПОСТКОВИДНЫХ НАРУШЕНИЙ И ЕГО ИММУНОПАТОЛОГИЧЕСКИЕ МЕХАНИЗМЫ. РОЛЬ АУТОИММУНИТЕТА

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Поступила: 02.06.2021 **Одобрена: 12.08.2021** **Принята к печати: 17.09.2021**

Резюме: Все больше данных свидетельствуют о тесной связи между инфекцией COVID-19 и аутоиммунитетом. Термин «затяжной/отсроченный постковидный синдром» был предложен для обозначения стойких симптомов или последствий, персистирующих/развившихся в течение более 4 недель с момента появления острых симптомов COVID-19. Недавний метаанализ показал, что у 80% пациентов, инфицированных SARS-CoV-2, развился один или несколько долговременных симптомов. Выявлены психоневрологические, ревматологические, респираторные, сердечно-сосудистые, желудочно-кишечные и эндокринные проявления затяжного/отсроченного постковидного синдрома. Было показано, что распространенность большинства симптомов не снизилась, а даже возросла через 7–9 месяцев по сравнению с ранним периодом после выздоровления от острой инфекции. Возможные патогенетические звенья, влияющие на развитие синдрома, включают: (1) прямую вирусную инвазию или персистентность; (2) иммунологические нарушения и повреждения в исходе острого инфекционного воспаления; (3) ожидаемые последствия пребывания в критическом состоянии. Однако в большинстве случаев синдром пост-COVID-19 развился после нетяжелого течения острой инфекции COVID-19. Хотя нет никаких доказательств того, что какой-либо один механизм является общим для различных осложнений после COVID-19, можно предположить, что аутоантитела, которые обнаруживаются во время острого COVID-19, могут сохраняться и играть роль в развитии проявлений синдрома пост-COVID-19. Появление и прогрессирование симптомов в течение некоторого времени после разрешения острого COVID-19 подтверждает эту гипотезу. Распространенность нескольких патогенных аутоантител при остром COVID-19 сравнима с таковой при аутоиммунных заболеваниях. Некоторые аутоантитела сохраняются у таких пациентов не менее семи месяцев. Нами создан реестр пациентов с постострым синдромом COVID-19, который к апрелю 2021 года включает 81 случай. 77,8% этих пациентов — женщины. Средний возраст пациентов — 44 года (возрастной диапазон 11–77 лет). 79% пациентов не были госпитализированы во время острой инфекции (т.е. у них развился постострый синдром COVID-19 после легкой версии острого COVID-19). 74% пациентов отметили усталость/крайнюю усталость среди симптомов пост-COVID. В то время как 68% пациентов сообщили о симптомах постострого синдрома COVID-19 сразу после острой фазы инфекции, 38% испытали временное улучшение после острого COVID-19 до проявления постострых признаков COVID-19. Набор пациентов и анализ реестра продолжаются. Наш текущий исследовательский проект по постострому синдрому COVID-19 состоит из двух этапов. Первый этап участники могут пройти онлайн. Он включает в себя несколько анкетирований, онлайн-консультацию, компьютерную батарею нейропсихологических тестов и оценку физического состояния на основе некоторых функциональных маркеров, связанных с легочной и сердечно-сосудистой системами. Второй этап в Санкт-Петербурге предусматривает использование нескольких методов для оценки состояния тонких нервных волокон, микроциркуляции, профиля аутоиммунитета, функции вегетативной нервной

системы, периферического слуха и центрального звена слухового анализатора. Обосновывается растущая необходимость специализированного центра динамического наблюдения и реабилитации пациентов с пост-COVID, выполняющего также трансляционно-медицинские научные задачи.

Ключевые слова: COVID-19; аутоиммунитет; постковидный синдром; патогенез; лечение; реабилитация.

POST-COVID SYNDROME AND ITS IMMUNOPATHOLOGICAL MECHANISMS. THE ROLE OF AUTOIMMUNITY

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Received: 02.06.2021 **Revised: 12.08.2021** **Accepted: 17.09.2021**

Abstract: Increasing evidence suggests a strong association between the COVID-19 infection and autoimmunity. A term “post-acute COVID-19 syndrome” has been coined for the persistence of symptoms or development of sequelae beyond 4 weeks from the onset of acute symptoms of COVID-19. Recent meta-analysis revealed that 80% of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms. The neuropsychiatric, rheumatic, respiratory, cardiovascular, gastrointestinal, and endocrine manifestations were identified. It was shown that prevalence of the most symptoms have even risen in 7-9 months compared to the early recovery period. Potential mechanistic links contributing to the pathophysiology of postacute COVID-19 include: (1) direct viral invasion or persistence; (2) immunologic aberrations and inflammatory damage in outcome of acute infection; and (3) expected sequelae of post-critical illness. However, most cases of post-COVID-19 syndrome developed after non-severe COVID-19. While there is no evidence to put any single mechanism as common one for different post-COVID-19 complications, it can be suggested that autoantibodies, which are detected during acute COVID-19 can persist and play a role in the development of post-COVID-19 manifestations. The appearance and progression of symptoms for some time after resolution of acute COVID-19 favors this hypothesis. The prevalence of several pathogenic autoantibodies in acute COVID-19 is comparable to that in autoimmune diseases. Some autoantibodies persist in such patients at least for seven months. We established a patient registry of post-acute COVID-19 syndrome which includes 81 cases by April, 2021. 77,8% of these patients are women. The mean age of patients is 44 years old (age range 11–77 years). 79% of patients have not been hospitalized during acute infection (i.e. have developed post-acute COVID-19 syndrome following mild version of acute COVID-19). 74% of patients reported fatigue/extreme tiredness among their post-COVID symptoms. While 68% of patients have reported the symptoms of post-acute COVID-19 syndrome immediately after the acute phase of infection, 38% experienced temporary improvement after acute COVID-19 before the manifestation of post-acute COVID-19 signs. The enrollment of patients and the analysis of the registry is continuing. Our current research project on the post-acute-COVID-19 syndrome consist of two phases. The first phase can be passed online by the participants. It includes several questionnaires, online consultation, computer-based battery of neuropsychological tests and assessment of physical status based on some functional markers related to the pulmonary and cardiovascular system. The second phase can be conducted at outpatient clinic, using several methods to assess status of small nerve fibers, microcirculation, autoimmunity profile, autonomic nervous system function, peripheral hearing, and central auditory processing. The growing necessity in specialized center for the follow-up, dynamic observation and rehabilitation of post-COVID patientsis substantiated (intermingled with its translational biomedical research functions).

Key words: COVID-19; autoimmunity; post-COVID syndrome; pathogenesis; treatment; rehabilitation.

The immune response to SARS-CoV-2 appears to play a critical role in the disease pathogenesis and clinical manifestations. SARS-CoV-2 not only activates antiviral immune responses but can also cause excessive systemic action of pro-inflammatory mediators including cytokine release in patients with severe COVID-19, accompanied by lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities [1]. These SARS-CoV-2-induced immune abnormalities may result in the development of complicated infections by other microorganisms, severe multiple organ hypoperfusion, hypoxia and dysfunction and sometimes death.

Increasing evidence accumulated from the past year suggesting a strong association between the COVID-19 infection and autoimmunity. The reported inflammatory/autoimmune-related symptoms by patients, the appearance of circulating autoantibodies and the diagnosis of defined diverse autoimmune diseases in a subgroup of SARS-CoV-2-infected patients indicate the critical and pivotal effect of SARS-CoV-2 virus on human immunity, and its capability to trigger autoimmune disorders, in genetically predispose subjects [2].

Last year clinicians and scientist focused on the diagnosing and management of acute COVID-19. More recently, data have emerged that some patients continue to experience symptoms related to COVID-19 after the acute phase of infection. There is currently no clearly delineated consensus definition for the condition: terminology has included “long COVID”, “post-COVID syndrome” and “post-acute COVID-19 syndrome”. Among the lay public, the phrase “long haulers” is also being used. While the definition of the post-acute COVID-19 is evolving, it has been suggested to include persistence of symptoms or development of sequelae beyond 4 weeks from the onset of acute symptoms of COVID-19 [3].

Based on recent literature, it is further divided into two categories: (1) subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4–12 weeks beyond acute COVID-19; and (2) chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses [3].

Recent meta-analysis (which includes 18,251 publications and 47,910 patients) revealed that 80% of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms [4]. Neuropsychiatric, rheumatic respiratory, cardiovascular, gastrointestinal and endocrine manifestations were identified and the five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%).

One important question is whether post-COVID-19 sequela successfully resolve with time or persist (at least in a subgroup of patients). Peluso et al. showed that more that 40% of patients still reported fatigue in 7–9 months after acute COVID-19 resolution and prevalence of the most symptoms including trouble sleeping, concentration problems, fatigue, joint pain, back pain, nausea, dizziness, vision problems, cough, palpitations, diarrhea, rash and menstrual cramps have even risen in 7–9 months compared to the early recovery period (3–10 weeks) [5].

Potential mechanisms contributing to the pathophysiology of post-acute COVID-19 include: (1) direct viral invasion or persistence; (2) immunologic aberrations and inflammatory damage in response to the acute infection; and (3) expected sequelae of post-critical illness [3]. While the latter is well-recognized, most cases of post-COVID-19 developed after non severe COVID-19.

While there is no evidence for any hypothesis of post-COVID-19 syndrome’s pathogenesis, it can be suggested that autoantibodies, which are detected during acute COVID-19 can persist and play a role in the development of post-COVID-19 manifestations. The appearance and progression of symptoms some time after resolution of acute COVID-19 (see above) favors this hypothesis.

The prevalence of several pathogenic autoantibodies in acute COVID-19 is comparable to that in autoimmune diseases [6]. However, it is well-known that the titers of different autoantibodies increase during acute period of infectious disease. In a small study of nine COVID-19 patients published Jan. 25 2021 in the preprint server *medRxiv*, five had autoantibodies for at least seven months [7]. Interestingly, that autoantibodies were detected in 5/5 patients with reported persistent symptoms and 2/4 without continued symptoms.

In a preprint article Wang et al. used a novel high-throughput assay to quantitate circulating antibodies against 2,770 human proteins in individuals infected with SARS-CoV-2 and control subjects [8]. More proteins were targeted in infected individuals, and patients with severe COVID-19 exhibiting higher-level reactivity to the greatest number of antigens. Notably, autoantibody reactivities found in patients with COVID-19 included many that targeted immune-relevant proteins such as cytokines (for example, type I interferons), chemokines or their receptors, as well as particular leukocyte subsets (B cells, T cells, natural killer cells and monocytes). These antibodies had immunomodulatory effects in vitro and were associated with virological and immune parameters in vivo. Immune-targeting autoantibodies exacerbate disease severity in a mouse model of SARS-CoV-2 infection. If such autoantibodies persist, they can be partly responsible for the development of post-COVID-19 syndrome.

We established a patient registry of post-acute COVID-19 syndrome on 2/04/21 and as at 18/04/21 it includes 81 patients. 77,8% of patients are women. The mean age of patients is 44 years old (age range 11–77 years). 79% of patients have not been hospitalized during acute infection (i.e. have developed post-acute COVID-19 syndrome following mild acute COVID-19). 74% of patients reported fatigue/extreme tiredness among their symptoms. While 68% of patients have reported the symptoms of post-acute COVID-19 syndrome immediately after the acute phase of infection, 38% of patients experienced temporary improvement after acute COVID-19 before the manifestation of post-acute COVID-19 syndrome. The enrollment of patients and the analysis of the registry is continuing.

Our current research project on the post-acute-COVID-19 syndrome consist of two phases. The first phase can be passed online by the participants. It includes several questionnaires, online

Modalities of therapy

Dependent on the multisystem investigation:

– intravenous immunoglobulin;
– efferent therapy (plasmapheresis and immunoadsorption);
– vitamins D and C;
– anti-H1 and anti-H2 antihistamines;
– anticoagulants;
– ivermectin;
– breathing exercises;
– intravenous laser blood irradiation, ozone therapy;
– acupuncture;
– olfactory training;
– correction of liver dysfunction;
– antihypertensive therapy;
– antidepressants (SNRIs, tricyclics);
– cough suppressants;
– beta-1-blockers/beta-2 agonists for autonomic nervous system dysfunction;
– correction of the hormonal status (prolactin inhibitors, euthyroid achievement, corticosteroids in case of autoimmune/autoinflammatory phenomena);
– complex treatment of polyneuropathy;
– metronidazole and probiotics in case of secondary colitis/dysbiosis;
– complex treatment of chronic fatigue syndrome (sleep medications, pain medications, drugs to treat orthostatic intolerance and drugs for cognitive dysfunction, pentoxifylline, CoQ10 + NADH, L-carnitine, quercetin, epigallocatechin, curcumin, saffron, Astragali Radix and Salviae Miltiorrhizae Radix, Androhraphis, metformin, PPAR agonists, isoprinosine, hydroxychloroquine, low-dose naltrexone);
– biofeedback, cognitive behavioral therapy (CBT), graded exercise therapy (GET), and adaptive pacing therapy (APT);
– COVID-19 vaccination

Bench-to-bedside approach



Fig. 1. Suggested treatment modalities in long COVID syndrome/post-COVID complications

consultation, computer-based battery of neuropsychological tests and assessment of physical status based on some functional markers related to the pulmonary and cardiovascular system. The second phase can be conducted in Saint Petersburg. We have several methods to assess small nerve fibers, microcirculation, autoimmunity profile, autonomic nervous system function, peripheral hearing, and central auditory processing.

Even if the number of COVID-19 cases worldwide will tend to decrease, the incidence of post-COVID complaints and complications will nevertheless grow up substantially in the close perspective. That's why it is necessary to establish specialized multidisciplinary centers for medical aid to post-COVID patients (both as regards to somatic and psychic complaints) in order to organize appropriate dynamic observation, regular check-ups of their health status and rehabilitation combining it with translational research for the comprehension of post-COVID syndrome clinical pathophysiology. Several possible ways of immunomodulation and other treatment may be involved (Figure 1).

It can be achieved at outpatient clinics with stationary facilities for short staying, multisystem investigation and one-day efferent therapy [9], best of all — settled within university hospitals and/or high-tech medical centers. Several proposals of this kind are already coined and discussed elsewhere [9–11].

FUNDING

This work is supported by the grant of the Government of the Russian Federation for the state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

REFERENCES

1. Yang L., Liu S., Liu J. et al. COVID-19: immunopathogenesis and Immunotherapeutics, Signal Transduct. Target. Ther. 2020; 5: 1–8. https://doi.org/10.1038/s41392-020-00243-2.
2. Halpert G., Shoenfeld Y. SARS-CoV-2, the autoimmune virus, Autoimmun. Rev. 2020; 19: 102695. https://doi.org/10.1016/j.autrev.2020.102695.
3. Nalbandian A., Sehgal K., Gupta A. et al. Post-acute COVID-19 syndrome, Nat. Med. 2021; 27: 601–15. https://doi.org/10.1038/s41591-021-01283-z.
4. Lopez-Leon S., Wegman-Ostrosky T., Perelman C. et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv [Preprint]. 2021. https://doi.org/10.1101/2021.01.27.21250617.
5. Peluso M.J., Kelly J.D., Lu S. et al. Rapid implementation of a cohort for the study of post-acute sequelae of SARS-CoV-2 infection/COVID-19. medRxiv [Preprint]. 2021. https://doi.org/10.1101/2021.03.11.21252311.
6. Wei Gao Z., Zhong Zhang H., Liu C., Dong K. Autoantibodies in COVID-19: frequency and function, Autoimmun. Rev. 2021; 21: 102754. https://doi.org/10.1016/j.autrev.2021.102754.
7. Bhadelia N., Belkina A.C., Olson A. et al. Distinct Autoimmune Antibody Signatures Between Hospitalized Acute COVID-19 Patients, SARS-CoV-2 Convalescent Individuals, and Unexposed Pre-Pan-

demic Controls. medRxiv [Preprint]. 2021. https://doi.org/10.1101/2021.01.21.21249176.
8. Wang E.Y., Mao T., Klein J. et al. Diverse Functional Autoantibodies in Patients with COVID-19. Nature. 2021 May 19. https://doi.org/10.1038/s41586-021-03631-y. Epub ahead of print.
9. Ladds E., Rushforth A., Wieringa S. et al. Developing services for long COVID: lessons from a study of wounded healers. Clin Med (Lond). 2021; 21: 59–65. https://doi.org/10.7861/clinmed.2020-0962. Erratum in: Clin Med (Lond). 2021; 21(2):160.
10. Raza M.A., Aziz S., Shahzad S., Raza S.M. Post-COVID Recovery Assessment Clinics: A Real Need of Time. Innov Pharm. 2021; 12: 10.24926/iip.v12i1.3693. https://doi.org/10.24926/iip.v12i1.3693.
11. Gainetdinov R.R., Bornstein S. Update on Management of COVID-19 and Post COVID-19. Proceedings of the XXIV International Biomedical Conference of Young Researchers “Fundamental Science and Clinical Medicine. Homo and Health” 24 April 2021, Saint Petersburg State University. Fundam. Nauka & Clin. Med. 2021; 24: 952.

ЛИТЕРАТУРА

1. Yang L., Liu S., Liu J. et al. COVID-19: immunopathogenesis and Immunotherapeutics, Signal Transduct. Target. Ther. 2020; 5: 1–8. https://doi.org/10.1038/s41392-020-00243-2.
2. Halpert G., Shoenfeld Y. SARS-CoV-2, the autoimmune virus, Autoimmun. Rev. 2020; 19: 102695. https://doi.org/10.1016/j.autrev.2020.102695.
3. Nalbandian A., Sehgal K., Gupta A. et al. Post-acute COVID-19 syndrome, Nat. Med. 2021; 27: 601–15. https://doi.org/10.1038/s41591-021-01283-z.
4. Lopez-Leon S., Wegman-Ostrosky T., Perelman C. et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv [Preprint]. 2021. https://doi.org/10.1101/2021.01.27.21250617.
5. Peluso M.J., Kelly J.D., Lu S. et al. Rapid implementation of a cohort for the study of post-acute sequelae of SARS-CoV-2 infection/COVID-19. medRxiv [Preprint]. 2021. https://doi.org/10.1101/2021.03.11.21252311.
6. Wei Gao Z., Zhong Zhang H., Liu C., Dong K. Autoantibodies in COVID-19: frequency and function, Autoimmun. Rev. 2021; 21: 102754. https://doi.org/10.1016/j.autrev.2021.102754.
7. Bhadelia N., Belkina A.C., Olson A. et al. Distinct Autoimmune Antibody Signatures Between Hospitalized Acute COVID-19 Patients, SARS-CoV-2 Convalescent Individuals, and Unexposed Pre-Pandemic Controls. medRxiv [Preprint]. 2021. https://doi.org/10.1101/2021.01.21.21249176.
8. Wang E.Y., Mao T., Klein J. et al. Diverse Functional Autoantibodies in Patients with COVID-19. Nature. 2021 May 19. https://doi.org/10.1038/s41586-021-03631-y. Epub ahead of print.
9. Ladds E., Rushforth A., Wieringa S. et al. Developing services for long COVID: lessons from a study of wounded healers. Clin Med (Lond). 2021; 21: 59–65. https://doi.org/10.7861/clinmed.2020-0962. Erratum in: Clin Med (Lond). 2021; 21(2):160.
10. Raza M.A., Aziz S., Shahzad S., Raza S.M. Post-COVID Recovery Assessment Clinics: A Real Need of Time. Innov Pharm. 2021; 12: 10.24926/iip.v12i1.3693. https://doi.org/10.24926/iip.v12i1.3693.
11. Gainetdinov R.R., Bornstein S. Update on Management of COVID-19 and Post COVID-19. Proceedings of the XXIV International Biomedical Conference of Young Researchers “Fundamental Science and Clinical Medicine. Homo and Health” 24 April 2021, Saint Petersburg State University. Fundam. Nauka & Clin. Med. 2021; 24: 952.