ИММУНООПОСРЕДОВАННЫЕ ЗАБОЛЕВАНИЯ У ПОСТКОВИДНЫХ ПАЦИЕНТОВ И ИХ СВЯЗЬ С НАРУШЕНИЕМ АКТИВНОСТИ СИСТЕМЫ КОМПЛЕМЕНТА

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Резюме. Пандемия новой коронавирусной инфекции COVID-19, вызванная вирусом SARS-CoV-2, привела к далеко идущим последствиям. Вызываемые им изменения в макроорганизме могут сохраняться более 6-12 месяцев после окончания острой фазы заболевания, формируя постковидные нарушения иммунной системы. Пациенты, перенесшие острый COVID-19 как в легкой, так и в тяжелой форме, страдают от различных проявлений постковидного синдрома. Однако выраженность этих проявлений весьма вариабельна. Целью настоящего исследования стала оценка влияния степени поражения легких в остром периоде COVID-19 на выраженность клинических проявлений постковидного синдрома на примере иммуноопосредованных симптомокомплексов: аутоиммунного, пролиферативного и аллергопатологии. Обследован 131 пациент, перенесший инфекцию SARS-CoV-2. Для исследования использованы анамнестические данные из амбулаторных карт пациентов. С помощью метода ИФА-диагностики определялись IgA, IgM, IgG, специфичные к SARS-CoV-2, фрагменты комплемента C1q, C3a, C5a. В ходе исследований выявлена связь между тяжестью постковидного синдрома и тяжестью острого течения COVID-19. Вирус SARS-CoV-2 способен активировать комплемент, и активация эта сохраняется длительно (более полугода), что объясняет наличие клинических проявлений постковидного синдрома у лиц, перенесших легкую острую форму COVID-19 без поражения легких по данным компьютерной томографии и не имеющих выявленных нами ранее фенотипов поражения иммунной системы (врожденного звена – снижение экспрессии CD46 на Т-лимфоцитах и снижение экспрессии CD46 на NK-клетках, и приобретенного – снижение уровня Т-цитотоксических лимфоцитов и нарушение уровня В-клеток $CD45^+CD3^-CD19^+CD5^+CD27^+$). Полученные данные свидетельствуют о том, что обследование пациентов, имеющих постковидный синдром, должно проводиться не только путем оценки их клинических характеристик, но и путем изучения состояния иммунной системы таких пациентов с целью постановки правильного диагноза и назначения этиологической и патогенетической терапии, в том числе иммунотерапии. Аутоиммун-

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ные, пролиферативные и аллергические заболевания напрямую связаны с нарушениями иммунной системы. Обобщая результаты данного исследования, можно сделать следующие выводы: 1. Тяжесть аутоиммунных нарушений в постковидный период напрямую не связана с тяжестью заболевания, а в большей степени связана с базисной кортикостероидной терапией (ГКС) как для лечения аутоиммунных процессов, так и для лечения COVID-19. Если ГКС не используются при аутоиммунном тиреоидите, то их применение в остром периоде инфекции впоследствии снижало количество рецидивов. Тогда как при ревматоидном артрите ситуация обратная: применение ГКС в остром периоде инфекции у пациентов, уже находящихся на базисной кортикостероидной терапии, впоследствии приводит к увеличению количества рецидивов у пациентов, перенесших ковидный. 2. У пациентов, перенесших COVID, выявлена тенденция к увеличению наиболее клинически тяжелой аллергопатологии: во-первых, во всех группах (52%) в постковидный период участились обострения таких патологий, как отек Квинке, крапивница, анафилаксия, васкулит, альвеолит, бронхиолит. Все это свидетельствует о том, что на ухудшение состояния этих пациентов в постковидный период повлияла перенесенная инфекция, вызванная вирусом SARS-CoV-2. Аллергические поражения кожи оказались на втором месте по частоте обострений – около 28%. 3. Отмечается тенденция к увеличению частоты обострений пролиферативных заболеваний у пациентов с более тяжелыми формами острой инфекции COVID-19. Также следует отметить, что процент таких пациентов достаточно высок – от 31,6% до 48%. 4. Вирус SARS-CoV-2 может влиять на активацию системы комплемента, что объясняет наличие клинических проявлений постковидного синдрома у лиц, перенесших острую форму COVID-19 в легкой форме без поражения легких по данным компьютерной томографии и не имеющих выявленных нами ранее фенотипов поражения иммунной системы. Полученные данные свидетельствуют о том, что обследование постковидных больных должно проводиться не только путем оценки их клинических характеристик, но и путем исследования состояния иммунной системы таких пациентов с целью постановки правильного диагноза и назначения этиологической и патогенетической терапии, в том числе иммунотерапии.

Ключевые слова: иммунная система, компьютерная томография, вирусная пневмония, система комплемента, инфекция SARS-CoV-2, постковидный синдром

IMMUNE-MEDIATED DISORDERS IN POST-COVID PATIENTS AND THEIR RELATIONSHIP WITH IMPAIRED COMPLEMENT SYSTEM ACTIVITY

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Abstract. The COVID-19 pandemic caused by the SARS-CoV-2 virus has led to far-reaching consequences. The changes caused in COVID-19 patients may persist for more than 6-12 months after acute phase of the disease promoting post-COVID disorders of immune system. Patients who have had acute COVID-19 in both mild and severe forms suffer from various manifestations of post-COVID syndrome. However, the severity of these manifestations is quite variable. The aim of the study was to assess the effect of lung damage extent in acute period of COVID-19 on the severity of clinical manifestations in post-COVID syndrome as exemplified by immune-mediated syndromes, i.e., autoimmune disorders, proliferative conditions, and allergopathology. 131 patients who had who had a history of SARS-CoV-2 infection were examined. Anamnestic data from outpatient cards of patients were used for the study. Using the ELISA diagnostics method, IgA, IgM, IgG specific to SARS-CoV-2, complement components C1q, C3a, C5a were determined. The studies revealed a connection between the severity of post-COVID syndrome and the severity of the acute COVID-19 course. The SARS-CoV-2 virus is able of activating complement, and this activation persists for a long time (more than six months). This finding explains presence of clinical manifestations of post-COVID syndrome in individuals

who have had a mild acute form of COVID-19 without CT-detected lung damage without phenotypes of immune system damage that we have previously identified (congenital – decreased expression of CD46 on T lymphocytes and decreased expression of CD46 on NK cells, and acquired – decreased level of T-cytotoxic lymphocytes and impaired level of B-cells $CD45^{+}CD3^{-}CD19^{+}CD5^{+}CD27^{+}$). The data obtained indicate that the examination of post-COVID patients should be carried out not only by their clinical characteristics, but also by assessing markers of their immune system in order to make a correct diagnosis and prescribe etiological and pathogenetic therapy, including immune therapy. *Conclusions:* 1. Autoimmune, proliferative and allergic diseases are directly related to disorders of the immune system. The severity of autoimmune disorders in the post-COVID period is more associated with basic corticosteroid therapy (GCS) both for the treatment of autoimmune processes and for the treatment of COVID-19 (except of treating autoimmune thyroiditis). GCS treatment used in acute period of infection reduced the number of recurrenct disorders. The situation is the opposite in rheumatoid arthritis: the use of GCS in the acute period of infection in patients already on basic corticosteroid therapy subsequently leads to an increase in the number of relapses in post-COVID patients. 2. In post-COVID patients, we revealed a trend towards an increase in the most clinically severe allergopathology: firstly, in all groups (52%) in the post-COVID period, exacerbations of such pathologies as Quincke's edema, urticaria, anaphylaxis, vasculitis, alveolitis, and bronchiolitis became more frequent. These findings suggest that the worse condition of these patients in the post-COVID period was influenced by the past SARS-CoV-2 infection Allergic skin lesions were in second place in terms of the frequency of exacerbations (about 28%). 3. There is a tendency towards an increased frequency of proliferative diseases exacerbations in patients with more severe forms of acute COVID-19 infection. It should also be noted that the percentage of such patients is quite high, from 31.6% to 48%. 4. The SARS-CoV-2 virus may affect the complement activation system, thus explaining clinical manifestations of post-COVID syndrome in the persons who had a mild form of COVID-19 without evidence of lung damage immune system affection. Our data indicate that the examination of post-COVID patients should be carried out not only by assessing their clinical characteristics, but also by examining the state of the immune system in such patients in order to make a correct diagnosis and administer etiological and pathogenetic therapy, including immune therapy.

Keywords: immune system, computed tomography, viral pneumonia, complement system, SARS-CoV-2 infection, post-COVID syndrome

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Introduction

The COVID-19 coronavirus pandemic caused by the SARS-CoV-2 virus has had far-reaching consequences. According to case histories, patients with post-COVID syndrome experience severe fatigue, increased fatigability, an increase in the incidence of acute respiratory viral infections per year, an increase in the recurrence of skin diseases, allergy pathologies, an increase in the recurrence of chronic infectious and non-infectious diseases of various organs and systems. Patients were examined at least six months after recovery from acute COVID-19. Such persistent post-infectious consequences are known as post-COVID syndrome [7]. When assessing post-COVID syndrome, it is necessary to reveal the main clinical symptoms of multiorgan pathology characteristic of post-COVID patients according to the literature [3]. For example, 410 participants in a Swiss study were assessed for complaints 7-9 months after being diagnosed with COVID-19, of which 39.0% of patients reported long-term symptoms such as fatigue (20.7%), loss of taste or smell (16.8%), shortness of breath (11.7%), and headache (10.0%), including among young, previously healthy people [6]. In another study by Chinese scientists, 1,733 patients were examined 6 months after acute COVID-19, in which 9% reported a long-term sensation of palpitations and 5% reported chest pain [2]. Cognitive impairments were noted, manifested by difficulty concentrating, deteriorating memory, perception, and/or speech reproduction [8]. In a study by Chinese scientists, approximately a quarter of patients reported anxiety, depression, and sleep disturbances

6 months after COVID-19 [2]. However, reports of similar complaints after mild COVID-19 suggest a contribution to their development by dysfunction of the autonomic nervous system [1]. Long-term cognitive impairment has been noted in studies aimed at assessing the condition of patients who have suffered critical illnesses; it occurs in 20-40% of patients hospitalized with COVID-19 [10]. Ruggeri R.M. et al. (2021) write about subacute thyroiditis with clinical manifestations of thyrotoxicosis weeks after the disappearance of respiratory symptoms [9]. COVID-19 can lead to the manifestation of latent autoimmune thyroiditis in the form of new-onset Hashimoto's thyroiditis [11] or Graves' disease [5]. Endocrine manifestations of post-COVID syndrome can be a consequence of direct damage by the virus, immunological and inflammatory damage, as well as iatrogenic complications.

Thus, in the literature there are indications of various clinical pathological manifestations of post-covid syndrome, but at the same time, there is no systematization of these studies, and there is no data on the pathogenesis of the formation of clinical manifestations of post-covid syndrome. In addition, if the immune system of patients with acute coronavirus infection has been studied quite well, then the state of the immune system of post-covid patients remains practically unstudied. All this served as the basis for our studies of post-covid patients.

The aim of the study was to assess the impact of the degree of lung damage in the acute period of COVID-19 on the severity of clinical manifestations of post-COVID syndrome using the example of immune-mediated symptom complexes – autoimmune, proliferative, and allergopathology.

Materials and methods

A total of 131 patients who had recovered from SARS-CoV-2 infection were examined. Of these, 48 were men aged 20 to 76 years (mean age 55.3 years) and 83 were women aged 21 to 79 years (mean age 53.4 years). The inclusion criteria in the study groups were: confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction (PCR), the presence of IgA, IgM to the SARS-CoV-2 virus in the acute and post-acute periods of infection and IgG to the SARS-CoV-2 virus during the recovery period, computed tomography data of the lungs on the presence or absence of changes of the "ground glass" type. This study was conducted at least 6-12 months after the infection caused by SARS-CoV-2. All patients were preliminarily examined by a general practitioner and an immunologist-allergist in order to identify concomitant diseases, as well as by doctors of other specialties before COVID-19 to establish concomitant diagnoses. The groups were randomized by gender, age, concomitant diseases according to the χ^2 criterion. All studies were approved by the Independent Local Ethics Committee at the State Autonomous Healthcare Institution of the Republic of Chelyabinsk "City Clinical Hospital No. 1" of Chelyabinsk (protocol No. 8 dated 04/11/2022), on the basis of which these studies were conducted, and by the Independent Local Ethics Committee at the Federal Research Institute of Virology and Infection "Virom" of Rospotrebnadzor of Yekaterinburg, protocol No. 1 dated 03/22/2024, on the basis of which these studies were conducted.

Clinical research methods

– Identification of persons with post-COVID syndrome after examination by doctors: therapist, allergist-immunologist, pulmonologist, ENT doctor.

– Filling out the immunological examination card.

– Physical, laboratory and instrumental examinations for diagnosis.

Immunological research methods

ELISA diagnostic methods. Determination of the level of specific IgA, IgM, IgG to the SARS-CoV-2 coronavirus, C1 inhibitor, C3a and C5a complement components by enzyme immunoassay and immunofluorescence analysis on a Multiscan FC Thermoscientific enzyme immunoassay analyzer (China). The study was conducted using generally accepted standardized enzyme immunoassay methods (test systems of VectorBest, Russia; Cytokine LLC, Russia).

Statistical research methods

Based on the study results, a database was created in Excel (MS Office 2007). Data processing and analysis were performed using R 3.1.1 12 (RFoundation for Statistical Computing, Vienna, Austria) and Microsoft Excel version 14.0. Student's t-tests were used for parametric data; differences were considered significant at $p < 0.05$.

Equipment

The following equipment was used: Multiscan FC Thermoscientific enzyme immunoassay analyzer (China), Mindray SL-1200 A immunochemiluminometer (China), related equipment (centrifuges, shakers, thermostats, etc.), computers with software packages required for mathematical and statistical analysis of the results.

Results and discussion

According to the data presented in Table 1, reliable differences were obtained between groups KT0 and KT1-2, as well as KT0 and KT3-4 – the frequency

TABLE 1. SEVERITY OF CLINICAL MANIFESTATIONS OF THE AUTOIMMUNE SYMPTOM COMPLEX IN POST-COVID PATIENTS DEPENDING ON THE DEGREE OF LUNG DAMAGE IN THE ACUTE PERIOD OF COVID-19

Diseases with increased incidence of relapses or first identified after clinical recovery from acute COVID-19 infection/ degree of lung damage according to CT data	Total number of patients examined (n = 131)		Group 1 CT 0 (n = 38)		Group 2 CT 1-2 (n = 68)		Group 3 CT 3-4 (n = 25)	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Rheumatoid arthritis	30	22.9	4	10.2	19	27.9 $p_{1-2} < 0.05$	7	28.0
Autoimmune thyroiditis	20	15.3	11	29.0	7	10.3 $p_{1-2} < 0.05$	2	8.0 $p_{1-3} < 0.05$

Note. Reliability of differences between groups p_1-p_2, p_1-p_3, p_2-p_3. Differences $p < 0.05$ (Student's T-test) were considered reliable.

TABLE 2. SEVERITY OF CLINICAL MANIFESTATIONS OF THE SYMPTOM COMPLEX OF ALLERGOPATHOLOGY IN POST-COVID PATIENTS DEPENDING ON THE DEGREE OF LUNG DAMAGE IN THE ACUTE PERIOD OF COVID-19

Diseases with increased incidence of relapses or first identified after clinical recovery from acute COVID-19 infection/degree of lung damage according to CT data	Total number of patients examined (n = 131)		Group 1 CT 0 (n = 38)		Group 2 CT 1-2 (n = 68)		Group 3 CT 3-4 (n = 25)	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Eczema, contact dermatitis, psoriasis	36	27.5	11	29.0	18	26.7	7	28.0
Quincke's edema, urticaria, anaphylaxis, vasculitis, alveolitis, bronchiolitis	68	51.9	20	52.3	35	51.5	13	52.0
Seasonal rhinitis, conjunctivitis	32	24.4	10	26.3	17	25.0	5	20.0
Bronchial asthma	19	14.5	4	10.5	14	20.6	1	4.0

Note. As for Table 1.

of exacerbations of rheumatoid arthritis in the post-COVID period is significantly higher in the group with lung damage of less than 50% in the acute period of COVID-19 compared to the group of patients without lung damage, while the frequency of exacerbations of autoimmune thyroiditis is significantly higher in patients without lung damage in the acute period of COVID-19 compared to the other groups.

When analyzing the effect of the degree of lung damage in the acute period of COVID-19 infection on the increase in the frequency of exacerbations of allergic diseases in the post-COVID period (Table 2), no dependence was found. However, at the same time, a tendency towards an increase in the most clinically severe allergopathology was revealed in post-COVID patients: firstly, in all groups (52%), exacerbations of such pathologies as Quincke's edema, urticaria, anaphylaxis, vasculitis, alveolitis, and bronchiolitis became more frequent in the post-COVID period. All this indicates that the deterioration of the condition of these patients in the post-COVID period was influenced by the infection caused by the SARS-CoV-2 virus. Allergic skin lesions were in second place in terms of exacerbation frequency – about 28%.

TABLE 3. SEVERITY OF CLINICAL MANIFESTATIONS OF THE PROLIFERATIVE SYMPTOM COMPLEX IN POST-COVID PATIENTS DEPENDING ON THE DEGREE OF LUNG DAMAGE IN THE ACUTE PERIOD OF COVID-19

Diseases with increased incidence of relapses or first identified after clinical recovery from acute COVID-19 infection/degree of lung damage according to CT data	Total number of patients examined (n = 131)		Group 1 CT 0 (n = 38)		Group 2 CT 1-2 (n = 68)		Group 3 CT 3-4 (n = 25)	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Frequent lymphadenitis	41	31.3	13	34.2	20	29.4	8	32.0
Benign tumors: fibroids, cysts, polyps, fibroadenomas, endometriosis	54	41.2	12	31.6	30	44.1	12	48.0

Note. As for Table 1.

TABLE 4. ANALYSIS OF COMPLEMENT SYSTEM PARAMETERS IN POST-COVID PATIENTS DEPENDING ON THE DEGREE OF LUNG DAMAGE ACCORDING TO COMPUTED TOMOGRAPHY DATA IN THE ACUTE PERIOD OF COVID-19

Degree of lung damage according to CT data / Level of complement system indicators	Group 1 CT0 (n = 38) M±m, p	Group 2 CT 1-2 (n = 68) M±m, p	Group 3 CT 3-4 (n = 25) M±m, p	Group 4 Conditionally healthy individuals who have not had COVID-19 (n = 16) M±m, p
C1q, mcg/mL	273.9±31.7	275.5±27.9	199.1±20.3 $p_{1-3} < 0.05$ $p_{2-3} < 0.05$ $p_{3-4} < 0.05$	287.2±31.2
C3a, ng/mL	109.7±6.4	115.3±6.9	106.3±13.0	119.7±18.3
C5a, ng/mL	27.2±3.5 $p_{1-4} < 0.05$	25.2±2.6 $p_{2-4} < 0.05$	27.1±5.9 $p_{3-4} < 0.05$	15.1±2.7

Note. As for Table 1.

The frequency of exacerbations of proliferative diseases did not show significant differences between patient groups depending on the degree of lung damage in the acute period of infection (Table 3), but there was a tendency for the frequency of exacerbations to increase in patients with more severe forms of acute COVID-19 infection. It should also be noted that the percentage of such patients is quite high – from 31.6% to 48%. These data further indicate that post-COVID patients develop multiple organ pathology.

One of the key indicators of immune status is the complement system. Disturbances in the activity of the complement system can lead to serious consequences for various organs and tissues – the central nervous system, liver, lungs, and the immune system as a whole [4]. Therefore, the next stage of the study was to compare the level of complement system indicators in post-COVID patients depending on the severity of acute coronavirus infection (Table 4).

As can be seen from Table 4, all patients who have had COVID-19 have increased activity of the complement fragment C5a, which indicates long-term (at least six months) stimulation of the classical complement activation pathway. Also noteworthy is the persistent decrease in the activity of C1q, which is responsible for the normalization of activated complement, in the most clinically severe patients.

Conclusions

Autoimmune, proliferative and allergic diseases are directly related to disorders of the immune system.

Summarizing the results of this study, we can make the following conclusions:

1. The severity of autoimmune disorders in the post-COVID period is not directly related to the severity of the disease, but is more associated with basic corticosteroid therapy (GCS) both for the treatment of autoimmune processes and for the treatment of COVID-19. If GCS are not used for autoimmune thyroiditis, then their use in the acute period of infection subsequently reduced the number of relapses. Whereas with rheumatoid arthritis, the situation is the opposite: the use of GCS in the acute period of infection in patients already on basic corticosteroid therapy subsequently leads to an increase in the number of relapses in post-COVID patients.

2. In post-COVID patients, a tendency towards an increase in the most clinically severe allergopathology was revealed: firstly, in all groups (52%) in the post-COVID period, exacerbations of such pathologies as Quincke's edema, urticaria, anaphylaxis, vasculitis, alveolitis, and bronchiolitis became more frequent. All this indicates that the deterioration of the condition of these patients in the post-COVID period was influenced by the past infection caused by the SARS-CoV-2 virus. Allergic skin lesions were in second place in terms of the frequency of exacerbations – about 28%.

3. There is a tendency towards an increase in the frequency of exacerbations of proliferative diseases in patients with more severe forms of acute COVID-19 infection. It should also be noted that the percentage of such patients is quite high – from 31.6% to 48%.

4. The SARS-CoV-2 virus can affect the activation of the complement system, which explains the presence of clinical manifestations of post-COVID syndrome in individuals who have had an acute form of COVID-19 in a mild form without lung damage according to computed tomography data and who do not have the phenotypes of immune system damage that we have previously identified. The data obtained indicate that the examination of post-COVID patients should be carried out not only by assessing their clinical characteristics, but also by examining the state of the immune system of such patients in order to make a correct diagnosis and prescribe etiological and pathogenetic therapy, including immune therapy.

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