ВЛИЯНИЕ ТЕЧЕНИЯ ОСТРОЙ ИНФЕКЦИИ COVID-19 НА ТЕЧЕНИЕ ПОСТКОВИДНОГО СИНДРОМА

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Резюме. Пандемия коронавирусной инфекции COVID-19, вызванная вирусом SARS-CoV-2, привела к глобальной заболеваемости и высокой смертности во всем мире. По данным историй болезни, длительное время (от полугода до 2-3 лет) после перенесенной острой инфекции COVID-19 у пациентов отмечается выраженная усталость, повышенная утомляемость, учащение случаев заболеваний ОРВИ за год, учащение рецидивов кожных заболеваний, аллергопатологий, обострение легочной патологии, заболеваний мочевыводящих путей, учащение рецидивов хронических инфекционных заболеваний, таких как герпесвирусная и папилломавирусная инфекции, утяжеление течения хронических сердечно-сосудистых и других соматических заболеваний разных органов и систем. Обследование пациентов проводилось не менее чем через шесть месяцев после выздоровления от острого COVID-19. Подобные стойкие постинфекционные последствия известны как постковидный синдром. Оценивая постковидный синдром, необходимо раскрыть основные клинические синдромы полиорганной патологии, характерной для постковидных пациентов. Эндокринные и кардиальные проявления постковидного синдрома могут быть следствием прямого повреждения вирусом, иммунологического и воспалительного повреждения, а также ятрогенных осложнений. Цель исследования – оценить влияние тяжести течения острого COVID-19 на течение постковидного синдрома. Задачи исследования: 1. Проанализировать выраженность клинических проявлений симптомокомплекса поражения сердечно-сосудистой системы у постковидных пациентов в зависимости от степени поражения легких в острый период COVID-19. 2. Проанализировать выраженность клинических проявлений патологии эндокринной системы, в том числе впервые выявленной, у постковидных пациентов в зависимости от степени поражения легких в острый период

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COVID-19. Так как статистически значимых различий по полу и возрасту выявлено не было, то все пациенты были разделены на группы по степени поражения легких в острый период COVID-19 согласно клиническим рекомендациям по диагностике и лечению новой коронавирусной инфекции. Данное исследование показало, что клиническая картина постковидного синдрома характеризуется выраженным разнообразием формирования полиорганной патологии, как впервые выявленной, так и проявляющейся в учащении обострений хронических заболеваний. Выводы: 1. Согласно полученным данным, достоверные различия получены между группами КТ0 и КТ1-2, а также КТ0 и КТ3-4: частота обострений заболеваний сердечно-сосудистой системы в постковидном периоде достоверно выше в группах с поражением легких в острый период COVID-19 по сравнению с группой пациентов без поражения легких. Эти данные говорят о том, что поражения сердечно-сосудистой системы напрямую связаны с тяжестью течения COVID-19, вирусной нагрузкой и выявлялись наиболее часто (68%) у постковидных пациентов, перенесших тяжелую коронавирусную инфекцию. 2. Согласно полученным данным, частота нарушений обмена глюкозы, в том числе и впервые выявленных, достоверно возрастала в постковидный период у пациентов с поражением легких в острый период инфекции, тогда как по заболеваниям щитовидной железы, за исключение АИТ, достоверных различий не обнаружено. Возможно, эти нарушения также связаны, с одной стороны, с применением кортикостероидной терапии в острый период коронавирусной инфекции, а с другой стороны, с нарушением работы регуляторных механизмов эндокринной и иммунной систем под воздействием вируса SARS-CoV-2, что еще раз подтверждает наши предположения о формировании полиорганной патологии у постковидных пациентов.

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

INFLUENCE OF CLINICAL FEATURES IN ACUTE COVID-19 INFECTION ON THE COURSE OF POST-COVID SYNDROME

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Abstract. The COVID-19 pandemic caused by the SARS-CoV-2 virus has resulted in global morbidity and high mortality rates worldwide. According to case histories, for a long time after acute COVID-19 infection (six months to 2-3 years), patients may experience a pronounced fatigue, increased tiredness, higher incidence of acute respiratory viral infections *per* year, increased recurrence of skin diseases, allergies, exacerbation of pulmonary disorders, urinary tract diseases, increased recurrence of chronic viral diseases, e.g., herpesvirus and papillomavirus infections, aggravation of chronic cardiovascular and other somatic diseases of various organs and systems. Patients were examined at early as six months after recovery from acute COVID-19. Such persistent post-infectious consequences are referred to as post-COVID syndrome. When assessing post-COVID syndrome, it is necessary to identify the main clinical syndromes of multiorgan pathology characteristic of post-COVID patients. Endocrine and cardiac manifestations of post-COVID syndrome may be a consequence of direct damage from viral infection, immunological and inflammatory damage, as well as iatrogenic complications. Objective of our study was to assess the impact of acute COVID-19 severity on the course of post-COVID syndrome. The research objectives were as follows: 1. To analyze the severity of clinical manifestations of cardiovascular disorders in post-COVID patients depending on the degree of lung damage in the acute period of COVID-19 (CT0 to CT4). 2. To analyze the severity of clinical manifestations of endocrine disorders, including newly diagnosed pathology, in post-COVID patients depending on the degree of lung damage in acute period of COVID-19. Since we did not found any significant gender-and age-dependent differences, all patients were divided into groups by the degree of lung damage during acute

period of COVID-19, according to clinical guidelines for the diagnosis and treatment of a new coronavirus infection. This study showed that the clinical picture of post-COVID syndrome is characterized by a pronounced diversity in development of multiple organ pathology, both newly diagnosed, or manifesting by increased frequency of exacerbations of chronic diseases. Conclusions: 1. According to the data obtained, reliable differences were obtained between groups CT0 and CT1-2, as well as CT0 and CT3-4: the frequency of exacerbating cardiovascular disorders in the post-COVID period is significantly higher in groups with lung damage over acute period of COVID-19 compared to the group of patients without lung damage. These data suggest that cardiovascular disorders are directly related to the severity of COVID-19, viral load, and were detected most frequently (68%) in post-COVID patients who initially had a severe coronavirus infection. 2. According to our results, the frequency of glucose metabolism disorders, including those detected for the first time, proved to be significantly increased in the post-COVID patients with lung damage during acute infection. Meanwhile, no significant differences were found for thyroid disorders, except of autoimmune thyroiditis (AIT). These disorders may be associated with usage of corticosteroid therapy in acute period of coronavirus infection, or with impairment of regulatory mechanisms of the endocrine and immune systems induced by SARS-CoV-2 virus, thus again confirming our assumptions concerning development of multiple organ pathology in post-COVID patients.

Keywords: immune system, computed tomography, viral pneumonia, 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]. R.M. Ruggeri et al. 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, M 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, M, G 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 Vector-Best, 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 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.

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.

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 CT 0 (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.

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%.

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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