УДК 616.98:578.834.1]-07-097
https://doi.org/10.20538/1682-0363-2024-2-46-54

Clinical and immunological characteristics of post-COVID syndrome

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ABSTRACT

Aim. To evaluate changes in clinical manifestations and the cytokine profile of blood serum in patients with post-COVID syndrome.

Materials and methods. The study involved 46 patients (37 women and 9 men) with signs of post-COVID syndrome 1–12 months after COVID-19 infection. COVID-19 infection was laboratory-confirmed (patients were tested positive for SARS-Cov-2 RNA using polymerase chain reaction (PCR), or they were tested positive for SARS-Cov-2 immunoglobulin (Ig)G antibodies after the end of the acute phase and in asymptomatic infection). Along with mandatory tests included in the regular health checkup of medical staff, the levels of interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, tumor necrosis factor alpha (TNFα), interferon gamma (INFγ), and total IgE were determined in the blood serum of patients.

Results. The results showed that the development of post-COVID syndrome did not depend on the age and gender of patients and the severity of the acute phase of infection. Patients were more likely to develop post-COVID syndrome in the absence of antiviral therapy or in case of its ineffectiveness. A high level and imbalance of pro- and anti-inflammatory cytokines without laboratory signs of inflammation underlie the development of clinical manifestations at early stages of post-COVID syndrome (up to 3 months). The clinical presentation was characterized by symptoms of asthenia and functional disorders in the nervous, cardiovascular, and respiratory systems and gastrointestinal tract. After 3 months, the content of most cytokines returned to normal levels, whereas only the concentration of IL-17 remained elevated. Allergic and autoallergic mechanisms of damage to the skin, respiratory organs, and joints, as well as progression of cardiovascular pathology determined the clinical symptoms of post-COVID syndrome for 3–12 months.

Conclusion. The changes in the cytokine profile over 12 months reflect different damage mechanisms at different periods of the post-COVID syndrome, which determines the range of its clinical manifestations.

Keywords: post-COVID syndrome, asthenic syndrome, cytokines

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study

Conformity with the principles of ethics. All persons signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the National Ilizarov Medical Research Center for Traumatology and Orthopedics (Protocol No. 2 (72) of 07.10.2022).

For citation: Zhdanova E.V., Rubtsova E.V., Kostolomova E.G. Clinical and immunological characteristics of post-COVID syndrome. *Bulletin of Siberian Medicine.* 2024;23(2):46–54. https://doi.org/10.20538/1682-0363-2024-2-46-54.

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Клинико-иммунологическая характеристика постковидного синдрома

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РЕЗЮМЕ

Цель – оценить динамику клинических проявлений и цитокиновый профиль сыворотки крови у пациентов с постковидным синдромом.

Материалы и методы. Обследовано 46 пациентов (37 женщин и 9 мужчин) с признаками постковидного синдрома спустя 1–12 мес после перенесенной инфекции COVID-19. Факт перенесенной инфекции COVID-19 был лабораторно подтвержден (положительный результат полимеразной цепной реакции РНК SARS-Cov-2 в анамнезе или положительный титр антител иммуноглобулина (Ig) класса G к SARS-Cov-2 после купирования острого периода и при бессимптомном течении инфекции). Наряду с обязательным перечнем исследований, предусмотренных порядком проведения обязательных периодических осмотров медицинских работников, в сыворотке крови пациентов определяли содержание цитокинов интерлейкина (IL) 1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, фактора некроза опухоли альфа (TNFα), интерферона гамма (IFNγ) и уровень общего IgE.

Результаты. Формирование постковидного синдрома не зависит от возраста, пола пациентов и тяжести течения острого периода перенесенной инфекции. При отсутствии противовирусной терапии или ее неполноценности вероятность развития постковидного синдрома повышается. В основе формирования клинических проявлений в ранние сроки – до 3 мес – постковидного синдрома лежит высокий уровень и дисбаланс про- и противовоспалительных цитокинов при отсутствии лабораторных признаков воспаления. Клиническая картина характеризуется симптомами астенизации и функциональными нарушениями нервной, сердечно-сосудистой, дыхательной систем и желудочно-кишечного тракта. Спустя 3 мес уровень большинства цитокинов нормализуется, но остается высокой только концентрация IL-17. Аллергические и аутоаллергические механизмы повреждения кожи, органов дыхания, суставов, а также прогрессирование сердечно-сосудистой патологии определяют клиническую симптоматику постковидного синдрома на протяжении 3–12 мес.

Заключение. Динамика цитокинового фона в течение 12 мес отражает различные механизмы повреждения в разные сроки постковидного синдрома, что и определяет спектр его клинических проявлений.

Ключевые слова: постковидный синдром, астенический синдром, цитокины

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все лица подписали информированное согласие на участие в исследовании. Исследование одобрено независимым этическим комитетом «Национальный медицинский исследовательский центр травматологии и ортопедии имени академика Г.А. Илизарова» (протокол № 2 (72) от 07.10.2022).

Для цитирования: Жданова Е.В., Рубцова Е.В., Костоломова Е.Г. Клинико-иммунологическая характеристика постковидного синдрома. *Бюллетень сибирской медицины.* 2024;23(2):46–54. https://doi.org/10.20538/1682-0363-2024-2-46-54.

INTRODUCTION

The pandemic caused by SARS-CoV-2, with its undulating course due to new mutations of the virus, led to the development of a chronic condition called "long COVID" [1]. About 20% of people who went through the acute phase of COVID-19 with completed replication of SARS-CoV-2 experience a combination of various clinical symptoms in the post-COVID period. They make up post-COVID syndrome [1–3] which affects up to 5 million people worldwide [4, 5].

Post-COVID syndrome (PCS) is included in ICD-10 (U09.9) as a condition after COVID-19 (Post COVID-19 condition, unspecified) with a time criterion of at least 12 weeks [6, 7]. Most patients in the post-COVID period tend to have normal laboratory and radiological parameters, which indicates that virological recovery has been achieved. Despite this, some patients do not return to their initial physical activity and do not notice a full recovery [8–10]. Particular attention should be paid to the fact that the development of PCS does not depend on age, gender differences, severity of the acute phase, and prior hospitalization, and symptoms can appear at different times after the disease.

Currently, in Russia, guidelines for rehabilitation measures after COVID-19 have been developed and introduced into clinical practice [6]. The proposed scale for individual rehabilitation routing of people who had COVID-19 determines the possibility of rehabilitation measures at various stages of medical care, in particular in the outpatient setting. The priority in this program is the recovery period of the first 3 months after the acute phase of coronavirus infection. The early start of rehabilitation is aimed at preventing complications and speeding up full recovery and return to the previous lifestyle.

However, some patients do not achieve full recovery even after 12 months, which significantly reduces their quality of life. In addition, in clinical practice, both the onset and progression of many chronic diseases are increasingly recorded not only in a period of up to 12 weeks but also after 3–8 months after the infection. In this regard, identifying the mechanisms of PCS formation is relevant and can serve as a basis for predicting the development of complications and justifying the prevention and correction of its manifestations.

The aim of the study was to evaluate changes in clinical manifestations and the cytokine profile of blood serum in patients with PCS.

MATERIALS AND METHODS

The analysis of the obtained data was carried out in the outpatient department of one of Tyumen healthcare facilities from January to May 2022. The study involved employees of this healthcare facility who underwent a regular health checkup (a total of 302 people, of which 204 were women). The mandatory list of examinations included an examination by an internal medicine physician, complete blood count and blood biochemistry (glucose, total cholesterol, HDL, LDL, triglycerides); ECG, chest fluoroscopy in accordance with the procedure approved by the Ministry of Healthcare of the Russian Federation for mandatory health checkups of medical workers who work with industrial health and safety hazards (Order of the Ministry of Healthcare of the Russian Federation No. 29N of 28.01.2021, as amended on 01.02.2022).

The study involved 46 patients (37 women and 9 men) with signs of asthenia 1–12 months after COVID-19 infection. They did not have somatic symptom disorders that could provoke or aggravate asthenia in the post-COVID period, which means that they represented health status group I–II. All of them had a laboratory-confirmed history of COVID-19 infection (a positive SARS Cov-2 RNA PCR or positive SARS Cov-2 IgG after the end of the acute phase and in asymptomatic infection).

The severity of COVID-19 infection in the acute phase was assessed according to the Temporary Guidelines for the Prevention, Diagnosis and Treatment of Novel Coronavirus Infection (COVID-19) (Ministry of Healthcare of Russia. Edition 17 (09.12.2022)). According to their medical history, 5 people had no symptoms in the acute phase of COVID-19; 26 individuals had mild symptoms, 10 – moderate and 5 – severe. The last acute phase of infection occurred 1–3 months ago (n = 12); 3–6 months ago (n = 18); 6–12 months ago (n = 16). 49% of those surveyed had COVID-19 more than twice over the past 2 years.

The content of interleukin (IL) -1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, tumor necrosis factor alpha (TNFα), and interferon gamma (INFγ) in the blood serum of patients with PCS was determined by enzyme immunoassay using a standard reagent kit (Protein Contour LLC, Russia). The analysis was carried out according to the manufacturer's instructions. The results were recorded on the Multiskan photometer (Labsystems, Finland). The parameters obtained from the study of serum from healthy blood donors (n = 25) were used as control values. The level of total IgE in blood serum was determined using the enzyme-

linked immunosorbent assay (ELISA) with the result recorded on the Multiskan SkyHigh microplate reader (Thermo FS, Finland).

The results were statistically processed using the Statistica 9 software package (StatSoft, USA). In order to choose the method for the statistical analysis, the Shapiro – Wilk test was used to check data for normality of distribution. Only one of the studied parameters had normal distribution. The data were presented as the median and the interquartile range Me [Q_{25}; Q_{75}]. The differences were analyzed using the nonparametric Mann – Whitney *U*-test. The differences between the groups were considered statistically significant at $p < 0.05$.

RESULTS

Asthenia as the main manifestation of PCS was more common in women (n = 37) than in men (n = 9). The average age of women was 49.43 [18.0; 73.0] years. The average age of men was higher – 57. 62 [31.0; 73.0] years (Table 1).

Table 1

Gender and age profile of patients with PCS

Parameter	Number of cases, *n* (%)	Age distribution
Men	9 (20%)	18–30 years old : 0 31–40 years old: 1 41–50 years old: 0 51–60 years old: 3 61–70 years old: 3 71 years and older: 2
Women	37 (80%)	18–30 years old: 5 31–40 years old: 6 41–50 years old: 10 51–60 years old: 9 61–70 years old: 3 71 years and older: 4

Basically, both men and women had mild symptoms in the acute phase of infection (57%, n = 26), receiving treatment in the outpatient setting. More than half of them (52%) did not receive antiviral therapy to the full extent, that is, they did not complete the course of antiviral therapy and/or did not always take antiviral drugs at a therapeutic dose or independently reduced the dose and/or volume of prescribed medications. Ten patients, most of them women, had a moderate course of the disease with a complication of interstitial pneumonia.

Five employees, three of whom were men, had severe COVID-19 infection. All patients with moderate and severe infection received treatment in hospital followed by an outpatient rehabilitation course. They completed a full course of etiotropic antiviral therapy. Five patients, four of whom were women, had no symptoms in the acute phase and learned about the history of COVID-19 only from a positive SARS-Cov-2 IgG.

During the first three months after the acute phase of COVID-19, younger people more often needed medical care, including 5 women aged 32.53 [31.0; 48.0] years (Fig. 1). On the contrary, after 3–6 months, men over 50 years of age complained more often about the deterioration of their general condition. During 6–12 months, the gender profile of patients was the same, but older people (52.3 [45.0; 73.0] years) noted deterioration of the condition more often (Fig. 2).

During the second or third month after acute infection, asthenia was the main sign in all patients (Fig. 3). Its main manifestations included severe unmotivated general weakness, rapid fatigue, and a decreased ability to work.

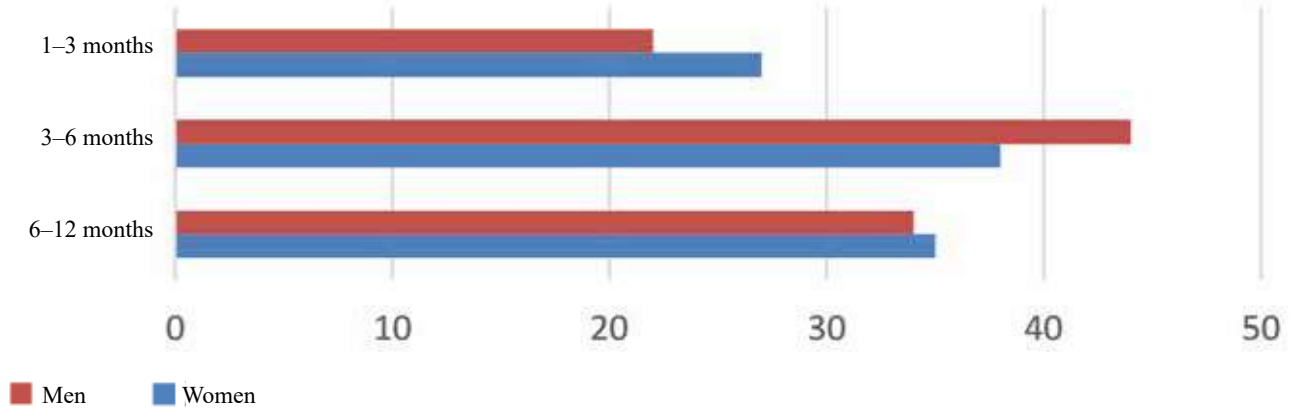

Fig. 1. Gender profile of patients with PCS depending on the duration of the acute phase of infection

Seven out of twelve patients complained of damage to the central nervous system in the form of persistent diffuse headaches, cognitive and mental disorders (sleep disturbance: insomnia at night and drowsiness during the day, vivid dreams, nightmares, short-term memory impairment, and inability to concentrate). In five patients, asthenia was accompanied by symptoms of cardiovascular system dysfunction, such as decompensation or the onset of cardiovascular diseases in the form of inappropriate tachycardia, increased or fluctuating blood pressure, and increased shortness of breath during habitual physical activity. Further examination (transthoracic echocardiography, 24-hour ECG) did not detect significant organic damage to the heart. Four patients complained of visual impairments in the form of a decrease in visual acuity, the appearance of blurry vision, and gritty and dry eyes. Signs of respiratory dysfunction persisted with the same frequency. There were single patient complains of skin rash in the form of polymorphic spots or pustular rash, dyspeptic disorders, and polyarthralgia.

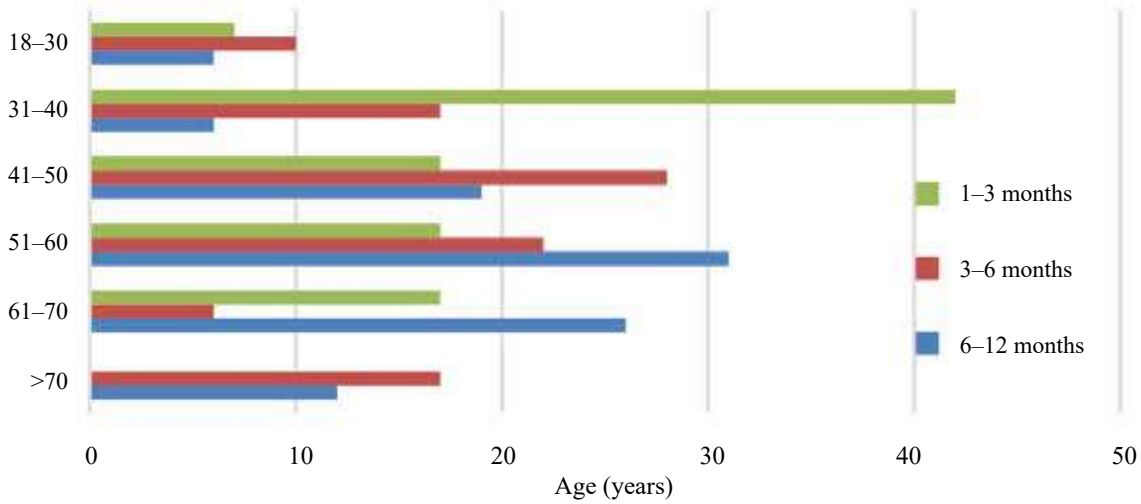

Fig. 2. Age profile of patients with PCS depending on the duration of the acute phase of infection

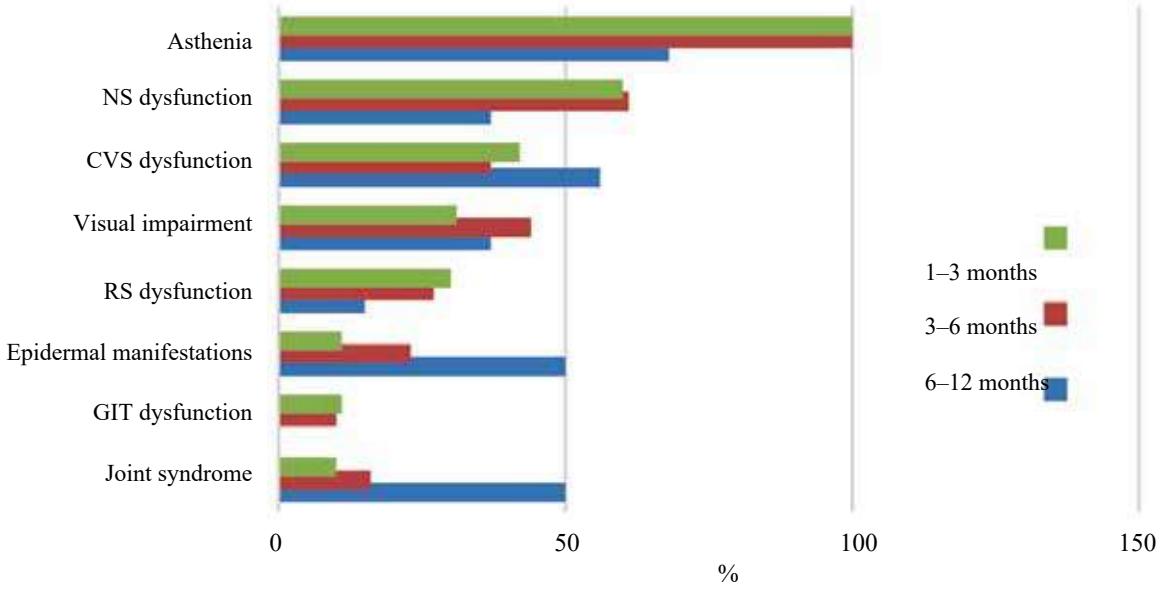

Fig. 3. Complaints of patients during various periods of PCS. NS – nervous system, CVS – cardiovascular system, RS – respiratory system, GIT – gastrointestinal tract

The analysis of the serum cytokine profile revealed high levels of all the studied cytokines in patients with PCS during a period of 2–3 months (Table 2). The median levels of IL-1ß and IL-2 were 1.3 and 1.4 times higher than those of healthy blood donors; IL-8 and IL-10 were 2 times higher, respectively. The content of IL-17 exceeded the control values by 2.8 times, IL-4 and IL-6 – by 3 and 4.5 times, respectively. The highest values were reached by TNFα and INFγ, whose concentrations exceeded the normal values by 5.5 and 70 times, respectively.

Table 2

Variability of serum cytokine levels in clinical groups depending on the duration of post-COVID syndrome, pg / ml, *Me* [Q_{25}; Q_{75}]

Parameter	Group 1, 1–3 months of PCS, *n* = 12	Group 2, 3–6 months of PCS, *n* = 18	Group 3, 6–12 months of PCS, *n* = 16	Group 4, healthy blood donors, *n* = 25	*p*		
					Groups 1–4	Groups 2–4	Groups 3–4
IL-1β	3.85 [3.45; 5.35]	2.62 [2.45; 3.05]	2.98 [2.45; 3.37]	2.88 [2.46; 3.12]	0.001	0.249	0.965
IL-2	0.18 [0.13; 0.26]	0.12 [0.09; 0.15]	0.13 [0.12; 0.14]	0.13 [0.09; 0.15]	0.002	0.484	0.655
IL-4	1.28 [0.98; 1.6]	0.37 [0.34; 0.52]	0.43 [0.38; 0.64]	0.42 [0.31; 0.55]	0.000	0.531	0.403
IL-6	3.77 [2.51; 4.64]	1.23 [1.12; 1.30]	0.98 [0.89; 1.17]	1.09 [0.97; 1.29]	0.000	0.363	0.129
IL-8	3.65 [2.85; 5.1]	1.66 [1.34; 2.67]	1.57 [1.36; 2.04]	1.6 [1.25; 2.42]	0.000	1.000	0.633
IL-10	2.48 [1.46; 3.22]	1.15 [1.08; 1.25]	1.2 [1.00; 1.27]	1.14 [1; 1.24]	0.001	0.686	0.720
IL-17	13.3 [11.16; 14.31]	5.74 [5.36; 6.99]	5.49 [4.88; 9.22]	4.75 [3; 5.61]	0.000	0.018	0.030
TNFα	1.7 [0.97; 2.65]	0.32 [0.25; 0.42]	0.25 [0.13; 0.46]	0.31 [0.17; 0.44]	0.000	0.919	0.467
INFγ	9.20 [0.67; 1.13]	0.14 [0.11; 0.15]	0.14 [0.10; 0.19]	0.13 [0.08; 0.08]	0.000	0.879	0.550

Despite the high levels of cytokines, there were no laboratory signs of inflammation in the complete blood count of patients with PCS: the values of the leukocyte content in peripheral blood were 6.12 [5.29; 7.29] × 10^9 / l; ESR 9.7 [4; 17] mm / h; C-reactive protein 6.9 [5.2; 11.3] mg / l. At the same time, an increase in the level of total IgE was recorded in 3 out of 12 people, who did not have a history of allergies and any clinical manifestations of allergies.

In the period of 3–6 months after the acute phase of COVID-19 ended, asthenia remained the main sign in all patients of the study group (100%). In 10 patients out of 18, manifestations of damage to the nervous system and gastrointestinal tract (nausea, increased and decreased appetite, disrupted taste preferences) were recorded. Symptoms of respiratory and cardiovascular dysfunction were present in 6 patients and, as a rule, were less severe and much easier to tolerate than in the early stages of PCS.

However, during this period, an increase in the number of patients (8 out of 18) with vision impairments was recorded. When examined by an ophthalmologist, 4 patients had changes in the fundus in the form of hypertensive and dystonic retinal angiopathy, and in half of the patients, these changes were recorded for the first time.

The number of patients with complaints of skin itching, petechiae, urticaria, and pustular rash increased to 4. Three patients had arthralgia and polyarthralgia, which debuted in two patients while in one patient cartilage destruction progressed.

The total IgE in the study group was 80.8 [25.0; 112.0] IU / ml and was significantly higher than in the control group (p = 0.009). An increase in total IgE was detected in 9 patients, which in 5 cases was accompanied by clinical symptoms of allergy in the form of atopic rash and bronchial obstructive syndrome.

The concentration of all the studied cytokines in patients at this stage of PCS decreased and often reached the values of healthy donors, but the IL-17 content remained significantly high at the level of 5.74 [5.36; 6.99] pg / ml versus 4.75 [3.0; 5.61] pg / ml in the controls (p = 0.018) (Table 2).

During 6–12 months after infection, clinical symptoms of PCS changed. Asthenia was diagnosed in 11 out of 16 patients, and signs of nervous system dysfunction were noted only in 6 cases. In 10 patients, persistent cardiac rhythm disturbances of various types and/or disturbances in myocardial repolarization (mainly in women) were recorded. Stabilization of arterial hypertension and formation of retinal angiopathy in 7 patients can be considered as signs of organic damage to the cardiovascular system.

Gastrointestinal disorders were not detected at this stage of PCS. Only 2 patients had shortness of breath when walking and mild cough as symptoms of impaired pulmonary function. However, two patients developed bronchial obstructive syndrome with persistent cough for the first time. In one case,

atopic asthma was diagnosed for the first time with a change in the spirogram manifested by a decrease in forced expiratory volume in 1 second (FEV1) / forced vital capacity (FVC) < 70%, FEV1 < 80% and a positive bronchodilator test (the increase while taking salbutamol was +12%).

Half of the patients (8 out of 16 cases) had changes in skin color in the form of pink and red spots, one patient had purple spots, and none of them sought medical help for this. These epidermal manifestations were identified during regular health checkup by a doctor. In one case, papulae were identified. Two patients had urticaria-like rash. One woman in the post-COVID period was newly diagnosed with recurrent urticaria in the form of pale pink and light red blisters, rising above the level of the skin and accompanied by itching. The patient had no history of allergy before COVID-19 infection. Antihistamine therapy did not have any clear effect. Subsequently, monoclonal gammopathy (Schnitzler syndrome) was diagnosed.

Over a period of 6–12 months, 8 patients had musculoskeletal impairments, the appearance or progression of which the subjects associated with COVID-19 infection. In 3 cases, it was isolated arthralgia or polyarthralgia without signs of joint damage according to the results of an ultrasound examination. In 3 patients, cartilage deformations and mixed arthritis with signs of synovitis were detected. In two patients, while receiving a full course of NSAIDs, chondroprotectors, intra-articular administration of corticosteroids, and physiotherapy, the destruction of the knee cartilage tissue progressed, which resulted in cartilage destruction and the development of aseptic necrosis and was an indication for knee arthroplasty.

The increase in allergic and autoallergic manifestations during 6–12 months of PCS was accompanied by an increase in the average IgE level in the blood to 98.98 [40.1; 172] IU, as well as in the relative and absolute content of eosinophils in peripheral blood (5.75 [3.2; 7.2]% and 0.54 [0.19; 0.76] $\times 10^9$ / l, respectively). In the meantime, acute-phase blood serum parameters did not exceed the established clinical norms. The blood cytokine profile was characterized only by a high level of IL-17, which was higher than that of donors (5.49 [4.88; 9.22] and 4.75 [3; 5.61] pkg / ml, respectively ($p = 0.03$)). The content of this cytokine depended on the clinical manifestations of PCS. In patients with isolated atopic epidermal manifestations, the concentration of IL-17 was 9.46 [6.20; 13.66] pkg / ml, in patients with musculoskeletal impairments, it was 12.56 [8.10; 14.56] pkg / ml, and in coexisting joint and epidermal syndromes, the parameter reached 13.95 [13.05; 14.05] pkg / ml.

DISCUSSION

Consequently, the clinical manifestations of PCS change dynamically during the year after acute infection, which is accompanied by natural changes in the plasma cytokine profile. The clinical symptoms of the first 3 months of PCS in the form of asthenia and CNS and cardiovascular dysfunctions are caused by an increased level and imbalance of both pro- and anti-inflammatory cytokines.

Cytokine levels gradually reach the normal range, which is accompanied by a decrease in the frequency of asthenia and CNS and respiratory dysfunction. However, after 3 months and further, only high levels of IL-17 are noted in the blood. Mast cells can intensely produce IL-17 [11], the activity of which increases in PCS [12, 13]. Moderate synthesis of IL-17 by T lymphocytes promotes the production of antimicrobial peptides. However, prolonged production of the IL-17 family can lead to chronic inflammation [14]. Perhaps a constant and long-term increase in IL-17 levels is associated with long-term post-COVID inflammation.

It is also likely that one of the factors activating mast cells is an increase in IgE. If its increase in the early stages of PCS was asymptomatic, then the increase in cases of hyperimmunoglobulin E syndrome and a rise in its values in the long term are already accompanied by clinical manifestations of allergies in the form of epidermal lesions and bronchial obstructive syndrome.

IL-17 is an important mediator of the formation of allergic and autoallergic damage, which is confirmed by significant differences in the degree of its increase depending on the localization of clinical manifestations and especially on their coexistence. It is known that IL-17 usually induces proinflammatory reactions, often associated with allergies, and also promotes the production of many other cytokines, chemokines, and prostaglandins [15]. IL-17 is assumed to play an important role in autoimmune diseases [16].

Most likely, an increase in the concentration of IL-17 also contributes to an increase in the incidence of visual impairments in the long term of PCS. High concentrations of IL-17 and increased levels of Th17 producing it have been found in a number of

ocular diseases associated with neovascularization [17]. The pathogenic role of IL-17 in the occurrence of joint syndrome has also been proven, which may be due to its participation in the formation of synovial inflammation with subsequent cartilage destruction [18].

Considering the ability of IL-17 to cause endothelial dysfunction and stimulate the activity of the renin – angiotensin – aldosterone system and arteriolar remodeling [19, 20], it is possible to explain the formation of stable hypertension and retinal angiopathy during 3–12 months of PCS. It is likely that the gradual recovery of gastrointestinal function is associated with the restoration of the gut microbiota and stimulation of the protection against bacterial and fungal pathogens by IL-17 [21].

CONCLUSION

Thus, the development of PCS does not depend on age and gender of patients and the severity of the acute phase of infection. However, patients are more likely to develop PCS in the absence of antiviral therapy or its inadequacy. The range of clinical manifestations of PCS changes over 12 months, which is determined by natural changes in the cytokine levels.

REFERENCES

1. Kostinov M.P., Markelova E.V., Svitich O.A., Polishchuk V.B. Immune mechanisms of SARS-CoV-2 and potential drugs for the prevention and treatment of COVID-19. *Pulmonologiya*. 2020;30(5):700–708 (in Russ.). DOI: 18093/0869-0189-2020-30-5-700-708.
2. Sudre C.H., Murray B., Varsavsky T., Graham M.S., Penfold R.S., Bowyer R.C. et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the COVID symptoms. *Study App.* 2020;27(4):626–631. DOI: 10.1038/s41591-021-01292-y.
3. Klitzman R.L. Needs to prepare for «post-COVID-19 syndrome». *Am. J. Bioeth.* 2020;20(11):4–6. DOI: 10.1080/15265161.2020.1820755.
4. Amenta E.M., Spallone A., Rodriguez-Barradas M.C., Sahly H.M., Atmar R.L., Kulkarni P.A. Post-acute COVID-19: an overview and approach to classification. *Open Forum Infect. Dis.*2020;7(12):ofaa509. DOI: 10.1093/ofid/ofaa509.
5. Altmann D.M., Boyton R.J. Decoding the unknowns in long COVID. *BMJ.* 2021;372:132. DOI: 10.1136/bmj.n132.
6. Fernández-de-Las-Peñas C., Palacios-Ceña D., Gómez-Mayordomo V., Cuadrado M.L, Florencio L.L. Defining post-COVID symptoms (post-acute COVID, long COVID, persistent post-COVID): an integrative classification. *Int. J. Environ. Res. Public Health.* 2021;18(5):2621. DOI: 10.3390/ijerph18052621.
7. Greenhalgh T., Knight M., A'Court M., Buxton M., Husain L. Management of post-acute COVID-19 in primary care. *BMJ.* 2020;370:m3026. DOI: 10.1136/bmj.m3026.
8. Nalbandian A., Sehgal K., Gupta A., Madhavan M.V., McGroder C., Stevens J.S. et al. Post-acute COVID-19 syndrome. *Nat. Med.* 2021;27(4):601–615. DOI: 10.1038/s41591-021-01283-z.
9. Amenta E.M., Spallone A., Rodriguez-Barradas M.C., Sahly H.M.E., Atmar R.L., Kulkarni P.A. Post-acute COVID-19: an overview and approach to classification. *Open Forum Infect. Dis*. 2020;7(12):509. DOI: 10.1093/ofid/ofaa509.
10. Arnold D.T., Hamilton F.W., Milne A., Morley A.J., Viner J., Attwood M. et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax.* 2021;76(4):399–401. DOI: 10.1136/thoraxjnl-2020-216086.
11. Noordenbos T., Blijdorp I., Chen S., Stap J., Mul E., Cañete J.D. et al. Human mast cells capture, store, and release bioactive, exogenous IL-17A. *J. Leukoc. Biol.* 2016;100:453–462. DOI: 10.1189/jlb.3HI1215-542R.
12. Kazama I. Stabilizing mast cells by commonly used drugs: a novel therapeutic target to relieve post-COVID syndrome? *Drug Discov. Ther*. 2020;14(5):259–261. DOI: 10.5582/ddt.2020.03095.
13. Weinstock L.B., Brook J.B., Walters A.S., Goris A., Afrin LB., Molderings G.J. Mast cell activation symptoms are prevalent in Long-COVID. *Int. J. Infect. Dis*. 2021;112:217–226. DOI: 10.5582/ddt.2020.03095.
14. Isailovic N., Daigo K., Mantovani A., Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. *J. Autoimmun*. 2015; 60:1–11. DOI: 10.1016/j.jaut.2015.04.006.
15. Chang S.H., Dong C. Signaling of interleukin-17 family cytokines in immunity and inflammation. *Cell. Signal.* 2011;23:1069–1075. DOI: 10.1016/j.cellsig.2010.11.022.
16. Kostareva O.S., Gabdulkhakov A.G., Kolyadenko I.A., Garber M.B., Tishchenko S.V. Interleukin-17: functional and structural features; use as a therapeutic target. *Advances in biological chemistry.*2019;59:393–418 (in Russ.). DOI: 10.1134/S0006297919140116.
17. Li Y., Zhou E. Interleukin-17: role in pathological angiogenesis in ocular neovascular diseases. *Tohoku Journal of Experimental Medicine*. 2019;247(2):87–98. DOI: 10.1620/tjem.247.87.
18. Miossec P. Update on interleukin-17: a role in the pathogenesis of inflammatory arthritis and implication for clinical practice. *RMD Open.* 2017;3(1):e000284. DOI: 10.1136/rmdopen-2016-000284.eCollection 2017.
19. Nguyen H., Chiasson V.L., Chatterjee P., Kopriva S.E., Young K.J., Mitchell B.M. Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension *Cardiovasc. Res*. 2013;97(4):696–704. DOI: 10.1093/cvr/cvs422.
20. Orejudo M., Garcia-Redondo A.B., Rodrigues-Diez R.R., Rodrigues-Diez R., Santos-Sanchez L., Tejera-Munoz A. et al. Interleukin-17A induces vascular remodeling of small arteries and blood pressure elevation. *Clin. Sci. (Lond.).* 2020;134(5):513–527. DOI: 10.1042/CS20190682.
21. Yang Z.-J., Wang T.-T., Wang B.-Y., Gao H., He C.-W., Shang H.-W. et al. Deeper insight into the role of IL-17 in the relationship between hypertension and intestinal physiology. *J. Inflamm. (Lond.).* 2022;19(1):14. DOI: 10.1186/s12950-022-00311-0.

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Received 07.11.2023;
approved after peer review 27.11.2023;
accepted 26.12.2023