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РОЛЬ ЭКСТРАКЛЕТОЧНЫХ НЕЙТРОФИЛЬНЫХ ЛОВУШЕК В РАЗВИТИИ ПОСТКОВИДНОГО СИНДРОМА И ЕГО ОСЛОЖНЕНИЙ

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The Role of the Innate Immune System in the Development of Postcovid Syndrome and its Complications

Резюме

На сегодняшний день в мире актуальна проблема сохранения симптомов после выздоровления от новой коронавирусной инфекции. Клиническая картинка постковидного периода имеет множественные проявления: общие, респираторные, сердечно-сосудистые, желудочно-кишечные, кожные и другие симптомы. На данный момент не определены четкие лабораторные критерии, позволяющие установить диагноз данного состояния, но показана роль нейтрофилов в развитии как острого заболевания, так и постковидного синдрома. Образование нейтрофильных экстраклеточных ловушек (нетоз) является одним из патофизиологических механизмов течения новой коронавирусной инфекции. Кроме того, доказано влияние процесса нетоза на развитие осложнений в постковидном периоде. В статье обсуждается история термина, разнообразные клинические проявления постковидного периода, а также — роль механизмов врожденного иммунитета на всех этапах течения новой коронавирусной инфекции.

Ключевые слова: *коронавирусная инфекция, COVID-19, постковидный синдром, экстраклеточные нейтрофильные ловушки, нетоз, НЭЛ*

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Abstract

To date, the problem of preserving symptoms after recovery from a new coronavirus infection is urgent in the world. This condition is called postcovid syndrome. The clinical picture of postcovid syndrome has multiple manifestations: general, respiratory, cardiovascular, gastrointestinal, skin and other symptoms. At the moment, there are no laboratory criteria for the diagnosis of this condition, but the great role of neutrophils in the development of both acute disease and postcovid syndrome has been proven. The formation of neutrophil extracellular traps (not toz) is one of the pathophysiological mechanisms of the course of a new coronavirus infection. In addition, the effect of the ketosis process on the development of complications in the postcovid period has been proven. The article discusses the history of the term, various clinical manifestations of the postcovid period, as well as the role of innate immunity mechanisms at all stages of the course of a new coronavirus infection.

Key words: *coronavirus infection, COVID-19, postcovid syndrome, extracellular neutrophil traps, netosis, NETs*

Conflict of interests

The authors declare no conflict of interests

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Relevance

The epidemics of the novel coronavirus infection (COVID-19) started in the People's Republic of China in March 2019 and, according to the Johns Hopkins University, as of today, 217 countries have experience with this disease. The novel coronavirus infection is an acute respiratory viral disease caused by SARS-CoV-2 virus which affects primarily upper respiratory tract. The clinical forms of the disease are acute respiratory viral infection, atypical pneumonia without respiratory insufficiency, acute respiratory distress syndrome (pneumonia with acute respiratory failure), sepsis, septic shock, DIC, thrombosis, thrombembolia.

According to the official website Стопкоронавирус.рф for January 2023, approximately 21 million people are COVID survivors. Some patients still have symptoms of COVID-19 after clinical recovery. This condition is called post-COVID-19 syndrome; in foreign sources, it is called long COVID. The International Classification of Diseases, 10th Edition, now has several codes characterising the course of the post-COVID period in humans: U08.9, U09.9, U12.9.

The objective of this article is to present information on the post-COVID syndrome and its symptoms to healthcare practitioners. The article discusses the role of the inborn immunity and neutrophil extracellular traps in development of post-COVID syndrome and its complications. The review is based on full-text scientific publications from open sources (eLibrary, PubMed, Web of Science). The search depth was 4 years, starting from 2019. Analysis of available information makes it possible to conclude that post-COVID observation is essential for prevention of various complications.

Definition and Clinical Characteristics of Post-COVID Syndrome

The term "long COVID" was introduced by social network users to describe their own general state after the novel coronavirus infection. These data drew mass media's attention and after that the studies of such symptoms in patients were conducted [1].

One of the first studies was conducted in Italy with participation of patients who were followed up in outpatient settings after recovery from COVID-19. The study enrolled 143 patients with the mean age of 56.5 years old. The patients' condition was assessed on the average in 60.3 days after recovery. It was demonstrated that only 12.6 % of patients did not have any COVID-19-associated symptoms, while 32 % of patients had 1 or 2 symptoms, 55 % of patients suffered from 3 and more symptoms [2].

Following a literature review by Shin Jie Yong, various descriptions of post-COVID syndrome were identified (Table 1) [3].

According to the World Health Organisation, post-COVID syndrome is a condition in persons with potential or confirmed novel coronavirus infection, usually in 3 months after COVID-19 initiation, accompanied by symptoms which last at least for 2 months and cannot be attributed to an alternative diagnosis. Symptoms can be experienced for the first time, after recovery from COVID-19, or can persist after the previous disease. Also, symptoms can change or repeat over time [4].

According to the US Centers for Disease Control and Prevention, post-COVID condition is a wide range of emerging, persisting or current health problems which can be experienced in four and more weeks after

Table 1. *Definition and characteristics of postcovid syndrome*

Definition	Characteristic
Postcovid syndrome	Long-term COVID-19 disease, which is cyclical, progressive and multiphase Persistence of symptoms for more than 2 months The persistence of symptoms for more than 3 months from the moment of the first symptoms
Lingering covid	Multi-organ symptoms that persist for several months after acute COVID-19 The persistence of symptoms, for more than 100 days The persistence of symptoms for more than 4 weeks after the initial infection or diagnosis
Chronic postcovid syndrome	Multi-organ symptoms that persist for several months after acute COVID-19
Covid with residual phenomena	The persistence of symptoms, for more than 100 days
Late effects of SARS-CoV-2 infection	The persistence of symptoms for more than 4 weeks after the initial infection or diagnosis
COVID-19 Postactive syndrome	The persistence of symptoms for more than 4 weeks after the appearance of the first symptom
Acute postcovid symptoms	Persistence of symptoms for 5-12 weeks
Long-term postcovid symptoms	Persistence of symptoms for 12-24 weeks
Persistent postcovid symptoms	Persistence of symptoms for more than 24 weeks
Subacute COVID-19 Ongoing symptomatic COVID-19	Persistence of symptoms for 1-3 months from the moment of the first symptoms
Chronic COVID-19 syndrome	The persistence of symptoms for more than 3 months from the moment of the first symptoms
Long-term COVID syndrome	Persistence of symptoms for more than 3 months from the moment of the first symptoms

infection with COVID-19. It has been noted that even persons who previously had no COVID-19 symptoms during several days or weeks after infection, can have post-COVID conditions. Also, researchers classify post-COVID conditions into new symptoms or long-term symptoms, multisystemic consequences, including multisystem inflammatory syndrome and sequellae of hospitalisation, including post-ICU syndrome [5].

Specialists of the Moscow City Therapeutic Scientific Society identify the following processes during COVID-19 infection: asymptomatic process; acute process with various symptoms; long-lasting process associated with symptoms of acute infection and post-COVID syndrome, where new disease symptoms appear or regressed symptoms re-appear several months after recovery [6].

Clinical manifestations of post-COVID syndrome vary: respiratory symptoms (dyspnoea and cough), cardiovascular symptoms (chest tightness, headache, palpitations), general symptoms (fatigue, fever), neurological symptoms (cognitive disorders, headache, sleep disorders, dizziness), gastrointestinal symptoms (nausea, diarrhoea, abdominal pain, loss of appetite), skeletal muscle symptoms (joint and muscle pain), psychiatric symptoms (depression, anxiety), ENT disorders (ear pain, sore throat, anosmia), and skin rash [6-7].

According to Huang C et al. [8], 76 % of patients who participated in a large cohort study had at least one complaint during follow-up after dismissal from hospital (mean follow-up time after onset of symptoms was 186 days), and female patients had the highest number of complaints. The most common post-COVID symptoms were fatigue and muscle weakness (63 %), sleep disorders (26 %), anxiety or depression (23 %). It was found out that these symptoms had persisted for over 6 months after recovery.

The study by Niedziela JT et al. [9] enrolled 200 patients who had COVID-19 and did not have any severe comorbidities. Patients were divided into two groups depending on treatment regimen: at home (114 patients) and inpatient settings (86 patients). The rate of symptoms on the average in 105–107 days after the acute phase of the disease was similar in both groups and made 30.7 % in non-hospitalised patients and 38.4 % in hospitalised patients. The most common symptoms were anosmia, loss of taste, palpitations, fatigue and cough. The study groups did not have any differences in post-COVID symptoms.

The diagnosis of post-COVID syndrome is made only on the basis of an assessment of persistent or new symptoms after the infection, overall poor condition. There are no laboratory diagnostic criteria for this diagnosis. Also, the information on post-COVID syndrome duration and factors impacting its development are insufficient.

Role of Neutrophils in the Pathogenesis of Post-COVID Syndrome

One of the mechanisms of COVID-19 development is attraction and activation of neutrophils in the site of infection. Neutrophils are a type of leukocytes, blood granulocytes, that take an active part in inflammatory reactions. Varying composition of chemical granules of neutrophils allows them selecting numerous antibacterial strategies in sites of infection:

- Phagocytosis
- Degranulation
- Ability to form neutrophil extracellular traps (NETosis) [10].

Development of the novel coronavirus infection is associated with an increase in neutrophil/lymphocyte ratio, impacting the severity of the disease and clinical prognosis. Therefore, neutrophils and their effector mechanisms are becoming important mediators in COVID-19 immunopathogenesis [11].

At the beginning of the 21st century, V. Brinkmann et al. described a new strategy of the antibacterial effect of neutrophils — formation of net-like structures in extracellular space (neutrophil extracellular traps, NETs).

NETs are extracellular structures, similar to chromatin fibre networks, lined with highly active proteases and nuclear, cytoplasmic and granular proteins. Release of extracellular neutrophil traps during controlled neutrophil cell death (NETosis) can be caused by various inducers: microorganisms, bacterial components, activated platelets, complementary peptides, autoantibodies, interleukins (IL) IL-8, etc. [12].

There are several morphological forms of neutrophil extracellular traps; two of them are of most interest: network-like which is highly efficient in trapping pathogens and characterises an inflammation with favourable outcome; and thread-like which is observed in aseptic inflammation and can be a secondary alteration factor after enzymatic hydrolysis. In post-COVID period, a NET looks like an non-organised cluster of thin threads [13].

Extracellular traps were found in patients both in the acute period of the novel coronavirus infection and after recovery (refer to Table 2).

Table 2. *Results of studies related to the determination of the number of extracellular neutrophil traps or their products in patients with coronavirus infection*

Авторы/ Authors	**Период определения нейтрофильных экстраклеточных ловушек или их продуктов у пациентов/ Period of determination of neutrophil extracellular traps or their products in patients**	**Обнаруженные результаты/ Found results**
Fernández S. et al.	48-72 hours after hospitalization	Extracellular neutrophil traps
Zuo Y. et al.	1-25 day of hospitalization	Serum markers of extracellular neutrophil traps
Panda R. et al.	1st and 7th day of the disease	Serum markers of extracellular neutrophil traps
Eleonora Petito et al.	2-5 day of the disease	Serum markers of extracellular neutrophil traps
Masso-Silva JA et al.	1, 3, 5, 7, 9, 11 days of illness	Serum markers of extracellular neutrophil traps
Guéant JL et al.	4-14 day of the disease	Extracellular neutrophil traps
Kinnare N et al.	1-3 days of hospitalization	Serum markers of extracellular neutrophil traps
Кассина Д.В., и соавт	Day of hospitalization and up to 12 days after hospitalization	Extracellular neutrophil traps
Ng, H. et al.*	1-7 day of hospitalization, 4 months from the onset of the disease	Serum markers of extracellular neutrophil traps

Note. * The study of Ng, H. et al. [14] included 106 patients with moderate and severe COVID-19. When examining blood serum: levels of citrullinated histone H3, cell-free DNA, neutrophil elastase were elevated in patients with COVID-19 compared with healthy people. Subsequently, 55 patients were followed up for 4 months (median 122 [109-132] days) after acute illness. During this period, blood plasma was taken with the determination of serum markers of NEL, the content of which decreased to the level of healthy people after 4 months, while the work did not take into account the patient's well-being after recovery and the preservation or appearance of complaints

The paper by A. N. Kazimirskiy et al. [15] dedicated to comparison of clinical and laboratory characteristics of patients with post-COVID syndrome included 21 inpatient patients aged 18–59 years (36 [27÷50]) 1–3 months after the disease. 11 patients had mild disease, 7 patients had moderate disease and 3 patients had severe disease. A group of healthy controls comprised 20 patients aged 18–59 years (38.5 [29÷51.5]) without a history of coronavirus infection. The following parameters were elevated in blood biochemistry of patients with post-COVID syndrome: ALT (1.7 times), GGT (2.1 times) and alkaline phosphatase (3.7 times); the number of extracellular purine bases was elevated as well. Patients with a history of moderate coronavirus infection had a higher level of NETs vs. patients with mild disease; and patients who had severe disease did not have any traps [$p < 0.05$]. All patients in post-COVID period had one form of NETs: thin single threads, pointing out to active aseptic inflammation.

Role of NETosis in Development of Pathologic Disorders in Post-COVID Period

An active NETosis process results in unfavourable blood-clotting disorders and immunothrombosis. Excessive formation of extracellular neutrophil traps triggers a cascade of pathophysiological disorders in patients with a history of the novel coronavirus infection.

NETosis is activated by several mechanisms in the presence of SARS-CoV-2 virus. On the one hand, virus-infiltrated neutrophils directly induce NETosis and release NETs. On the other hand, exposure of neutrophils to SARS-CoV-2 boosts production of pro-inflammatory mediators (IL-8, IL-1β) by epithelial cells and macrophages, activating NETosis. Another path of NET production activation is virus-induced platelet activation which can enhance this process by interaction with neutrophils.

It was confirmed that, in septic conditions, formation of NETs and NETosis by-products act as direct inflammation enhancers: NETosis stimulates release of free DNA and by-products (e.g. elastases and histones). As a result, macrophages and endothelial cells express excessive amount of pro-inflammatory cytokines, which boost NETs production, thus forming a vicious circle of hyperinflammation in COVID-19. Hyperinflammation (also known as cytokine storm) is typical of COVID-19; it develops together with immunothrombosis and facilitates development of acute respiratory distress syndrome and extensive organ failure [16].

NET formation is a link between the processes of inflammation and clotting. Antimicrobial agents released during NET formation also activate platelets. Reaction of activated platelets and immune cells stimulates the clotting system and causes a related process which connects thrombotic and inflammatory paths [16]. Morphological blood clot substrate is neutrophil-generated cells which consist of decondensed thread-like chromatin. This is how the blood clot frame is formed and platelets and clotting are activated [17].

Statistically significant relations between system inflammation in COVID-19 and dramatic increase in the number of NET markers have been identified; assumptions have been made about their key role in the severity of acute respiratory distress syndrome, cardiovascular, renal and inflammatory manifestations on later stages of the disease. The study by Guéant JL et al. [18] enrolled 155 patients aged 25–86 years with confirmed novel coronavirus infection. Controls were 35 persons with a negative COVID-19 test. NET markers (neutrophilic elastase, myeloperoxidase DNA, histone DNA and double-stranded DNA) in the blood of outpatient and hospitalised COVID-19 patients were significantly higher vs. controls. There was an association between NET components and clinical manifestations and biomarkers of a severe disease.

Currently, global literature sources describe a few cases of confirmed relations between neutrophil extracellular traps and the course of post-COVID period. The main mechanisms of post-COVID syndrome development are as follows: virus persistence, persistent hyperinflammation, autoantibody production, changes in the homeostasis system with abnormal clotting. According to the authors, NETosis is a process ensuring the relation between the inborn immunity system, persistent inflammation, endothelial dysfunction, hemostasis and blood clotting [19].

The relationship between the processes of NET activation is confirmed by the study conducted by Pisareva E. [20], where 42 post-COVID-19 patients were followed up. Each of them had at least one symptom of post-COVID syndrome 6 months after discharge from ICU. Blood plasma tests demonstrated that serum marker levels of neutrophil extracellular traps in these patients were higher vs. healthy volunteers. It makes the author think that uncontrolled NET activation due to COVID-19 can be maintained by a feedback path resulting from release of system NETosis by-products.

According to Płazak W et al. [21], NET formation is one of the pathogenic mechanisms of clotting stimulation and enhanced atherosclerosis progression in patients after COVID-19, together with such

mechanisms as endothelial dysfunction, presence of aPL antibodies, complement system activation.

For patients in post-COVID period, several hypotheses were made regarding persistent blood thickening, affected by a number of pathophysiological factors: persistent inflammation, autoantibody production, virus-activated leukocytes and platelets, causing persistent inmmatory reaction. In post-COVID period, the following is observed: persistent blood clotting sustained by persistent activation of endothelial cells and platelets and enhanced fibrinous clot formation [22]. Thus, this process results in emergence of a group of patients who have symptoms after recovery from COVID-19 and develop cardiovascular complications. Thus, for instance, the total rate of blood clotting (including arterial and venous complications) on day 30 after discharge was 2.5 % (95 % confidence interval 0.8–7.6) [23]. Large cohort studies also conform this hypothesis: during 12 months after COVID-19, the patients had an increased risk of such cardiovascular complications as acute cerebrovascular event, heart rhythm disorders, myocarditis and pericarditis, complications of coronary heart disease [24].

Scharf RE et al. [25] noted that the mechanisms of post-COVID syndrome development include virus persistence and impaired adaptive immunity, NET formation, hyperinflammation and homeostasis activation. The immunological disbalance in post-COVID period is also discussed by Islam MS et al. [26]; they note that SARS-CoV-2 proteins directly react with immune mediators, resulting in impaired production of type 1 interferon and enhanced neutrophil activation. They introduced the term "NETinjury" to denote a cascade of immunological reactions including NETosis and bleeding disorder which cause organ microclotting.

Appearance of such symptoms as fatigue, muscle pain and cognitive disorders after recovery from COVID-19 can also be associated with excessive NETosis. Possible mechanisms of a cerebrovascular event are related to blood clotting and include inhibitors of angiotensin converting enzyme 2 (inhibitor of ACE2) — mediated endothelial damage, reduction in ACE2 inhibitor levels, acute inflammation and bleeding disorder associated with an infection, formation of NETs and aPL antibodies, hyperglycemia and acute stress [27].

Schematic presentation of pathological disorders in post-COVID period and their association with NETosis is as follows (refer to Figure 1).

A lot of experts note the significance of neutrophils in pathogenesis of arterial hypertension [28] and their higher level during the entire period of hospitalisation in patients with COVID-19 and arterial hypertension [29].

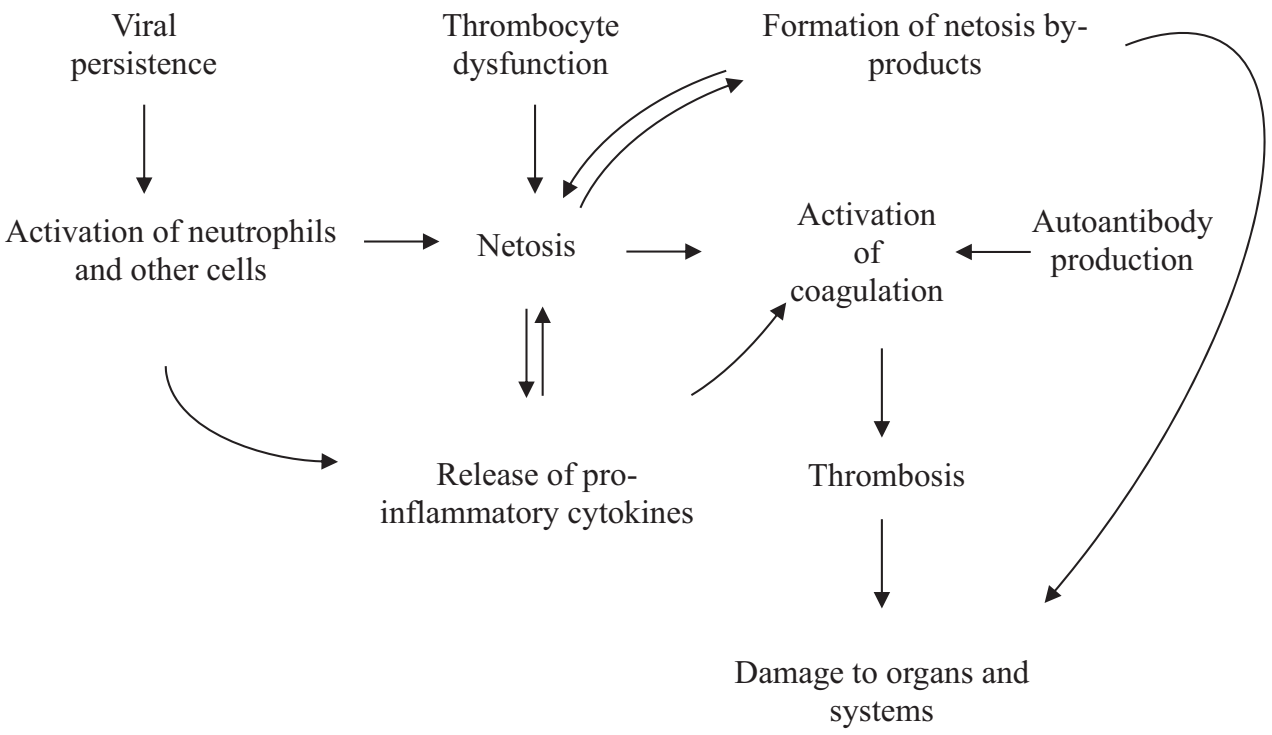

Figure 1. *The relationship of pathological disorders in the postcovid period*

NETosis directly affects chronic diseases; NETs are known to contribute as pro-hypertensive mediators in arterial hypertension. Besides, ACE2 inhibitor is a common receptor for the cardiovascular system and COVID-19 infection pathophysiology, as renin-angiotensin system inhibitors are first-line antihypertensive agents, and SARS-CoV-2 uses ACE2 inhibitors as a receptor for body penetration. When a patient with arterial hypertension is infected with COVID-19, reduced ACE2 inhibitor levels can cause inadequate immune response, including delayed pro-inflammatory cytokine storm, leading to neutrophil and macrophage infiltration and tissue damage. Once in the site of infection, neutrophils identify viral particles, and NET production is triggered, which is presumably a new mechanism of cardiovascular system damage after an infection [30].

Besides, a higher level of NETosis products is observed in patients with obesity and diabetes mellitus, and these conditions are thought to be pro-NETonic and can be associated with thrombotic complications [31].

A common feature of all post-COVID complications is involvement of organs which are closely related to the vascular and hemic system. The cardiovascular and respiratory systems are involved first of all. However, vessel wall inflammation and impaired clotting processes create conditions for tromboembolic episodes, involvement of other organs and systems, such as nervous system, GIT, liver and kidneys [32].

Conclusion

The real clinical practice and international scientific society confirm that a number of patients have persistent symptoms of the past novel coronavirus infection over a long period of time after clinical recovery. The pathogenesis of the post-COVID syndrome is based on a number of mechanisms, including a long-term inflammation resulting from formation of neutrophil extracellular traps — NETosis, a form of programmed cell death. The inflammatory status of a patient in post-COVID period can be evaluated on the basis of NETs blood count, requiring deeper studies in order to develop a therapy to mitigate negative consequences of NETosis.

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