NEUTROPHIL AND MONOCYTE EXTRACELLULAR TRAPS IN THE DIAGNOSIS OF POST-COVID SYNDROME

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Post-COVID syndrome (long covid, post COVID-19 condition) is characterized by cognitive and mental disorders, chest and joint pain, impaired sense of smell and taste, as well as by gastrointestinal and cardiac disorders. The diagnosis of post-COVID syndrome is based mainly on the patients' complaints. To date, no optimal diagnostic method has been proposed. The study was aimed to compare the informative value of the indicators obtained during conventional assessment of patients with post-COVID syndrome and the blood levels of neutrophil (NETs) and monocyte (METs) extracellular traps. The study involved neutropils and monocytes collected from 21 patients with post-COVID syndrome aged 18–59. Fluorescence microscopy and the SYBR Green (Evrogen) fluorescent dye for double-stranded DNA were used for enumeration and imaging of extracellular traps. Clinical and laboratory indicators make it impossible to identify the changes specific for post-COVID syndrome. At the same time, post-COVID syndrome is characterized by inflammation in the vascular endothelium. The filamentous forms of NETs found in blood are a laboratory feature of such aseptic inflammation. The filamentous forms of NETs have been detected only in those patients who have a history of mild to severe COVID-19, while the filamentous forms of METs have been found in patients having a history of severe infection. The findings show that the detection of the filamentous forms of NETs and METs in blood is the most informative diagnostic feature of post-COVID syndrome.

Keywords: post-COVID syndrome, diagnosis, neutrophil extracellular traps, monocyte extracellular traps, filamentous forms

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НЕЙТРОФИЛЬНЫЕ И МОНОЦИТАРНЫЕ ЭКСТРАКЛЕТОЧНЫЕ ЛОВУШКИ В ДИАГНОСТИКЕ ПОСТКОВИДНОГО СИНДРОМА

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Постковидный синдром характеризуется когнитивными и психическими нарушениями, болями в груди и суставах, нарушениями обоняния и вкуса, а также желудочно-кишечными и сердечными расстройствами. Диагностика постковидного синдрома основывается преимущественно на жалобах больных. В настоящее время оптимального метода диагностики не предложено. Целью исследования было сравнить информативность показателей, полученных при традиционном обследовании больных с постковидным синдромом, с уровнем в крови нейтрофильных (НЭЛ) и моноцитарных (МЭЛ) экстраклеточных ловушек. Исследовали нейтрофилы и моноциты, полученные от 21 больного в возрасте 18–59 лет с диагнозом постковидный синдром. Для визуализации и подсчета экстраклеточных ловушек использовали метод флуоресцентной микроскопии с применением флюоресцентного красителя для двухцепочечной ДНК SYBR Green (Evrogen). Клинико-лабораторные показатели не позволяют выявить специфичные для постковидного синдрома изменения. Вместе с тем, постковидный синдром характеризуется воспалительным процессом в сосудистом эндотелии. Лабораторным признаком такого асептического воспаления служат найденные нами в крови НЭЛ в нитевидной форме. Нитевидные структуры НЭЛ обнаружены только у тех больных, которые перенесли COVID-19 в легкой и среднетяжелой форме. А у больных, перенесших эту инфекцию в тяжелой форме, найдены нитевидные МЭЛ. Результаты исследования демонстрируют, что наиболее информативным диагностическим признаком постковидного синдрома является обнаружение в крови НЭЛ и МЭЛ в нитевидной форме.

Ключевые слова: постковидный синдром, диагностика, нейтрофильные экстраклеточные ловушки, моноцитарные экстраклеточные ловушки, нитевидные формы

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Post-COVID syndrome (long COVID, post-COVID-19 condition) is a novel poorly understood disorder. Despite the fact that there is no precise definition of post-COVID syndrome, many studies have shown that fatigue and dyspnoea are the most common symptoms that persist several months after the acute COVID-19 [1]. Other chronic manifestations of post-COVID-19 condition include cognitive and mental disorders, chest and joint pain, palpitations, myalgia, impaired sense of smell and taste, cough, headache, as well as gastrointestinal and cardiovascular disorders [2]. The post-COVID syndrome pathogenesisis is associated with damage to the large number of different cells and organs resulting in a whole range of symptoms. The long-term symptoms emerge in patients having a history of both mild and severe COVID-19. The symptoms of previous COVID-19 are diverse, however, they are not systematized.

Post-COVID syndrome most often gradually regress within half a year, however, multi-organ disorders persist over a long time and complications develop in some patients. The diagnosis of post-COVID syndrome is subjective, it is based on the patients' complaints.

Blood coagulation disturbances can be observed in the majority of patients showing a variety of symptoms. A D-dimer test for determination of the fibrin degradation product formed during enzymatic hydrolysis of the blood clot protein network is used for laboratory confirmation of hemostatic disorders associated with post-COVID condition [3, 4]. However, high D-dimer concentrations are not observed in all patients, that is why D-dimer cannot be considered the full-fledged and unique marker of post-COVID syndrome. Currently, there is no optimal diagnosis method allowing one to identify the informative pathogenetically significant diagnostic criteria of post-COVID syndrome.

Given the fact that the post-COVID syndrome pathogenesis is associated with cell damage resulting in inflammation, it has been suggested that the functional activity of the major inflammatory cells, neutrophils and monocytes, could be changed. Extracellular trap formation is a manifestation of the involvement of these cells in inflammatory response.

The study was aimed to compare the informative value of the indicators obtained during conventional clinical and laboratory assessment of patients with post-COVID syndrome and the results of blood testing for neutrophil and monocyte extracellular traps.

METHODS

A total of 21 outpatients aged 18–59 (36 [27÷50]) were enrolled. Inclusion criteria: the diagnosis of post-COVID syndrome. The comparison group (control group) included 20 healthy donors aged 18–59 (38.5 [29÷51.5]) who had no history of coronavirus infection.

Biochemical parameters of blood collected from patients and healthy donors were defined using the Olympus 5800 biochemical analyzer (JP, Olympus Corporation; USA) in the diagnostic laboratory of the Diagnostic Clinical Center № 1 of the Moscow Department of Health. The study was carried out in the laboratory of the Department of Physiology and Clinical Pathophysiology at the Faculty of General Medicine, Pirogov Russian National Research Medical University. All the procedures were performed in accordance with the adopted ethical standards. The new laboratory tests, i.e. determination of neutrophil and monocyte extracellular traps, were used during the study along with conventional clinical and laboratory tests.

Determining the levels of neutrophil and monocyte extracellular traps. Cell fractionation

Isolation of neutrophils and monocytes

The patients' venous blood was collected in the siliconized EDTA tubes for prevention of blood clotting. To isolate neutrophils and monocytes from venous blood treated with EDTA, blood was two-fold diluted with sodium phosphate buffer (pH 7.4) and layered on top of the Ficoll-verografin double density gradient medium. The top layer density was 1.077 g/cm^3, and the density of bottom layer was 1.190 g/cm^3. After centrifugation (1600 rpm, 30 min) neutrophils accumulated in the interface between the gradients (98–100% purity), and the monocyte ring appeared on the surface of the gradient medium top layer (1.077).

Neutrophils and monocytes were twice washed with sodium phosphate buffer (50 mmol, pH 7.4) to remove the Ficoll impurities. Sedimentation of blood cells was performed by centrifugation (1200 rpm, 15 min). The isolated neutrophils and monocytes in the RPMI-1640 medium were used for cell culture experiments. The viability of the isolated neutrophils and monocytes was 95 and 99%, respectively.

Immunofluorescence detection of neutrophil and monocyte extracellular traps

Fluorescence microscopy was used for detection and enumeration of neutrophil and monocyte extracellular traps. The method is explored in detail in the patent application RF No. 2021104936/14 (010852).

The results were presented as percentage, the ratio of the number of extracellular traps against the total number of cells in the field of view.

The neutrophil and monocyte extracellular traps were detected using the SYBR Green fluorescent dye (Evrogen; Russia) capable of specific interaction with double-stranded DNA. The cells and extracellular structures were enumerated and photographed at ×700 magnification.

Statistical processing

The STATISTICA 12.0 software package (StatSoft Ink.; USA) was used for statistical data processing. The results were reported as mean (M) and standard error of the mean or, when the distibution was non-normal, these were reported as median (Me) and the 25th and 75th percentile values of the distribution of indicator values (interquartile range). The quantitative characteristics were compared using the Mann–Whitney U test and the Kruskal-Wallis analysis of variance. The differences were considered significant at $p < 0.05$.

RESULTS

Initial assessment of the patients in the index group was performed between days 60 and 119 since the disease onset, i.e. after 95 [89–109] days or 13.6 weeks. The age of patients with post-COVID syndrome was 36.0 [27.0–50.0] years, while the age of healthy donors was 38.5 [29.0–51.5] years ($p = 0.818$). The patients and healthy donors had almost the same body mass index: 25.0 [22.0–28.7] kg/m^2 and 24.6 [23.3–29.5] kg/m^2 ($p = 0.783$), respectively.

A total of 11 patients (52.4%) had a history of mild disease, 7 patients (33.3%) had a history of moderate disease, and 3 patients (14.3%) had a history of severe disease. The COVID-19

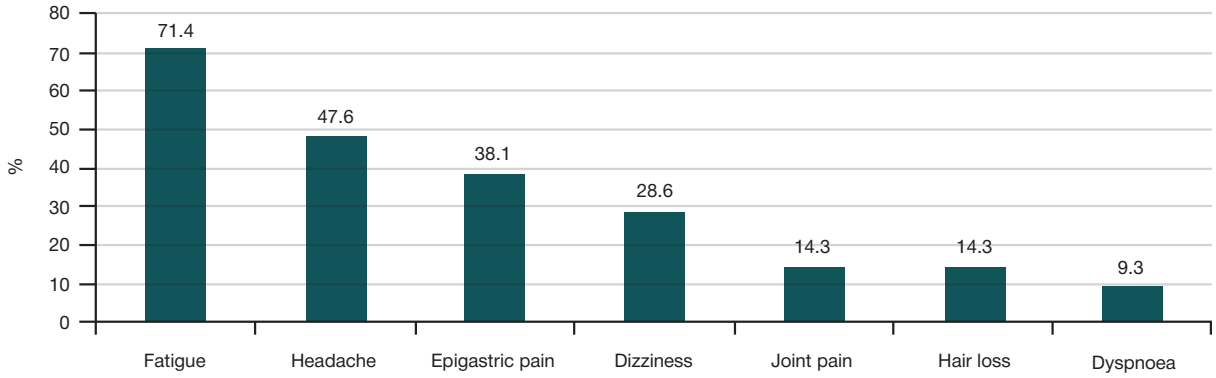

Fig. 1. Symptom occurrence in patients with post-COVID syndrome by day 95 [89–109] after the disease onset

symptom occurrence by day 95 [89–109] of the disease is provided in Fig. 1. On average, one patient had 1–6 symptoms (2.4 ± 1.1).

Fatigue, headache, epigastric pain, and dizziness were most often observed in the surveyed patients (Fig. 1). The patients less often complained of hair loss and dyspnoea. The other papers on the research of symptoms observed in patients with post-COVID syndrome most often report fatigue, myalgia, headache, and the symptoms of autonomic disorders. It can be assumed that such clinical features are most typical for post-COVID syndrome. The symptom cluster that does not require specific treatment possibly results from microangiopathy and vascular endothelial damage.

Laboratory parameters of patients with post-COVID syndrome compared to that of healthy donors are provided in Table.

Table. Laboratory parameters of patients with post-COVID syndrome and healthy donors

Parameters	Patients with post-COVID syndrome (*n* = 21)	Healthy donors (controls) (*n* = 20)	Probability *p*
	Me [25–75]	Me [25–75]	
Hemoglobin (g/L)	136,0 [127,0–157,0]	133,5 [130,0–147,5]	0,725
Mean corpuscular hemoglobin (pg)	29,6 [29,0–30,4]	30,7 [30,1–32,0]	0,005
Red blood cell distribution width (%)	13,5 [12,7–14,1]	12,4 [12,1–12,9]	0,015
Red blood cell count (10^{12}/L)	4,7 [4,5–5,1]	4,3 [4,1–4,7]	0,005
White blood cell count (10^9/L)	6,2 [5,7–8,1]	5,5 [4,6–6,8]	0,059
Neutrophils (10^9/L)	3,1 [2,5–4,8]	3,3 [2,2–4,4]	0,583
Lymphocytes (10^9/L)	2,2 [2,0–2,9]	1,8 [1,3–2,1]	0,001
Eosinophils (10^9/L)	0,2 [0,1–0,2]	0,1 [0,1–0,2]	0,0007
Platelet count (10^9/L)	264,0 [228,0–316,0]	261,0 [221,0–292,0]	0,464
Leukopenia, *n* (%)	0	3 (15)	0,179
Neutropenia, *n* (%)	2 (9,5)	1 (5)	0,965
Vitamin D deficiency, *n* (%)	7 (33,3)	8 (40)	0,658
Elevated D-dimer levels, *n* (%)	1 (4,8)	2 (10)	0,706
Erythrocyte sedimentation rate (mm/h)	5,0 [2,0–10,0]	7,5 [3,5–9,5]	0,57
Vitamin D (ng/mL)	17,3 [14,1–23,3]	23,0 [16,9–36,8]	0,211
Iron (μmol/L)	14,4 [9,4–22,9]	18,5 [14,5–24,6]	0,25
Ferritin (ng/mL)	35,4 [17,1–105,4]	97,3 [43,5–191,5]	0,229
Alanine transaminase (U/L)	25,8 [16,0–43,0]	15,5 [13,0–21,0]	0,007
Aspartate transaminase (U/L)	22,0 [20,5–27,4]	19,0 [16,0–22,0]	0,028
Gamma-glutamyltransferase (U/L)	33,0 [33,0–51,8]	15,5 [11,5–30,5]	0,031
Alkaline phosphatase (U/L)	213,5 [128,9–834,0]	58,0 [53,0–76,5]	0,018
Cholesterol (mmol/L)	5,3 [4,6–5,9]	5,4 [5,1–5,9]	0,612
Low-density lipoprotein (mmol/L)	3,4 [2,3–3,5]	3,1 [2,6–3,8]	0,719
Potassium (mmol/L)	4,7 [4,4–4,9]	5,0 [4,6–5,1]	0,328
Uric acid (μmol/L)	332,0 [277,0–465,0]	285,0 [213,5–345,5]	0,114
Urea (mmol/L)	4,7 [3,9–6,6]	4,0 [3,5–5,1]	0,116
Creatinine (mmol/L)	75,5 [64,5–80,5]	70,0 [54,0–82,5]	0,292
Thyroid-stimulating hormone (mIU/L)	1,5 [1,1–1,8]	2,0 [1,2–2,7]	0,177
Glucose (mmol/L)	5,2 [5,1–5,8]	4,6 [4,4–4,8]	0,0007
D-dimer (μg/L)	235,0 [190,0–300,0]	247,5 [192,0–361,5]	0,831

Note: Me — median value; [25–75] — interquartile range.

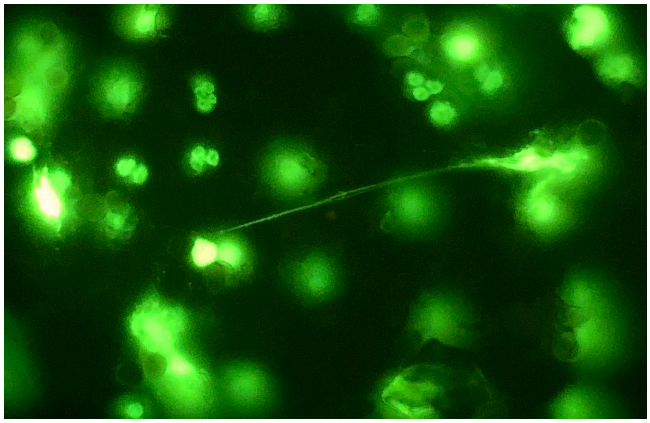

Fig. 2. Neutrophil extracellular traps in the form of single DNA filaments emerging from the neutrophil niclei in patients with post-COVID syndrome

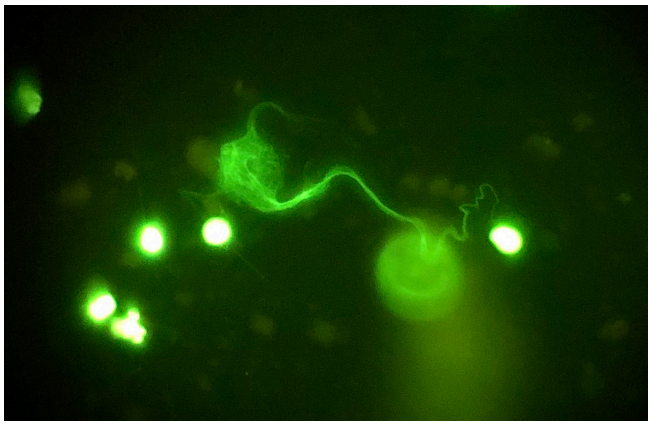

Fig. 3. Monocyte extracellular traps in the form of single DNA filaments emerging from the cell niclei in patients with post-COVID syndrome

Thus, the patients with post-COVID syndrome showed some relative increase in the red blood cell, lymphocyte, and eosinophil counts in peripheral blood compared to controls, along with elevated liver enzyme levels and blood glucose concentrations. Despite the fact that the changes in blood parameters observed in patients were within the reference ranges, these were clearly not accidental. In our opinion, the relative increase in red blood cell counts observed in patients having a history of COVID-19 was associated with concomitant hypoxia.

The increase in transaminase activity and blood glucose levels could be due to moderate hepatocyte damage.

This assumption is confirmed by the increase in the gamma-glutamyltransferase and alkaline phosphatase enzyme activity. In our opinion, the observed moderate increase in the eosinophil and lymphocyte counts reflects the hypothalamo-pituitary-adrenal axis fatigue during COVID-19 resulting in certain reduction of the surveyed patients' blood cortisol levels. The D-dimer levels in these patients remain virtually unchanged, which can be explained by no thrombogenesis or bland thrombogenesis.

DISCUSSION

The clinical and laboratory indicators provided in Table make it generally impossible to reveal specific changes characteristic of post-COVID syndrome. However, it is known that post-COVID syndrome is characterized by severe inflammation in the vascular endothelium [5]. The filamentous forms of neutrophil extracellular traps (NETs) detected in blood are considered a laboratory feature of such aseptic inflammation [6]. It is noteworthy that these filamentous structures are found only in those patients who have a history of mild to moderate disease (Fig. 2). The amount of NETs in those who experienced mild illness was 6.55 ± 0.94% ($p < 0.05$), while in moderate cases the amount of NETs was 0.86 ± 0.51% ($p < 0.05$). No METs were found in patients of these groups.

No NETs were revealed in patients having a history of severe COVID-19. However, DNA degradation products, the extracellular purine nitrogenous bases, were found in severe disease survivors [7]. We suggested the presence of the filamentous forms of METs and then detected those in such patients (Fig. 3). The levels of METs in these patients were low: 1.01 ± 0.71% ($p < 0.05$).

Enzymatic degradation of DNA filaments results in the emergence of factors of secondary alteration, the extracellular purine nitrogenous bases capable of damaging cells in the central nervous system (CNS) and internal organs, thus maintaining aseptic inflammation. Moreover, filamentous forms of extracellular traps and elevated levels of extracellular purine nitrogenous bases have been reported in patients with post-COVID syndrome for a long time (three months or more). We believe that elevated levels of extracellular purine nitrogenous bases are the most significant factor of the post-COVID syndrome pathogenesis that should be restricted in order to prevent damage to the endothelium, cells of the CNS and internal organs. The filamentous structures originating from neutrophils and monocytes constitute the source of these damaging molecules (factors of secondary alteration). Thus, effective therapy should be aimed at restriction of the neutrophil and monocyte extracellular trap formation in patients with post-COVID syndrome.

Currently, the majority of researchers define the extracellular structures produced by neutrophils (NETs) as the net-like structures and believe that neutrophils produce these net-like structures only. However, this is not true. We have for the first time revealed the relationship between the neutrophil extracellular trap morphology and the type of inflammation, we have also found that filamentous forms of NETs are unique to aseptic inflammation [6]. The net-like NETs are formed only in cases of the favorable course of inflammation caused by infection [6]. The net-like structure of NET is of special physiological significance, since it is functionally active. The filaments of such net capture pathogens and dying cells of the body, and then perform retraction [8]. Monocytes/macrophages absorb and hydrolyze the net together with the pathogens and the remains of dead cells. Filamentous forms of NETs are not capable of such responses and serve as a source of the factors of secondary alteration, the extracellular purine nitrogenous bases. Furthermore, adenin, that is increasingly released during the enzymatic hydrolysis of DNA filaments, inhibits T cells and can cause secondary immunodeficiency. Our findings make it possible to conclude that detection of filamentous forms of neutrophil and monocyte extracellular traps in blood is the most typical diagnostic feature of post-COVID syndrome.

CONCLUSIONS

Filamentous forms of neutrophil and monocyte extracellular traps are the diagnostic feature of post-COVID syndrome. Filamentous forms of neutrophil extracellular traps were found in patients with post-COVID syndrome who had a history of mild to moderate COVID-19. No neutrophil extracellular traps were found in patients with post-COVID syndrome who had a history of severe disease, however, filamentous forms of monocyte extracellular traps were detected in blood of these patients.

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