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Long-Term Effects of Covid-19 Clinical and Functional Characterization of Postcovid Syndrome and Approaches to Its Treatment

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Abstract. This article reviews the clinical and functional features of postviral syndrome as one of the most relevant consequences of the COVID-19 pandemic.

Particular attention is paid to long-term complications that persist in significant patients' number months after the acute period of infection, including respiratory, cardiovascular, and neurological and psychoemotional disorders.

On the basis of generalization of modern clinical observations and results of outpatient examinations, a systematization of symptom complexes forming the picture of the post-acute state is presented.

Pathogenetic mechanisms underlying long-term disorders, including chronic inflammation, vascular dysfunction and neurovegetative instability, are assessed. A separate section is devoted to therapeutic strategies aimed at restoring the functional reserves of the organism: approaches to drug correction, respiratory rehabilitation, neuropsychological support and multidisciplinary management of patients are included.

The conclusion substantiates the need to develop clinical protocols focused on a personalized approach to the treatment of postcoccygeal syndrome and its prevention in risk groups.

Keywords: COVID-19, post-COVID syndrome, prolonged COVID, respiratory complications, neurological disorders, psychosomatic disorders, cardiological complications, rehabilitation and recovery.

INTRODUCTION.

The COVID-19 pandemic caused by the SARS-CoV-2 virus has become an unprecedented global challenge not only for the health care system but also for the scientific community, highlighting the need for a comprehensive rethinking of approaches to diagnosis, treatment and follow-up of patients. Despite significant progress in controlling the acute course of the infection, clinical practice is increasingly recording cases of long-lasting symptoms and functional impairment in survivors, termed 'post-COVID' or 'long COVID'. These conditions not only reduce the quality of life of patients, but also create a significant socio-economic burden, especially in the context of overloaded outpatient health care and the growing number of patients with chronic disorders.

The pandemic of novel COVID-19 coronavirus infection has resulted in an unprecedented number of cases worldwide and a significant burden on health care systems. In addition to the acute course of the disease, the long-term consequences of the infection have received increasing attention in recent years.

It has been noted that despite recovery from acute COVID-19, some patients continue to have a complex of chronic symptoms called post-COVID-19 syndrome.

The term 'post-COVID' (synonyms: long COVID-19, long COVID) is used to refer to a cluster of symptoms and organ dysfunctions that persist or appear some time after acute SARS-CoV-2 infection. Generally, COVID refers to symptoms that persist for more than 12 weeks after the acute period of illness. According to the World Health Organization, postcovid syndrome occurs in about 6% of COVID-19 survivors, but the incidence is much higher among hospitalized patients, reaching 30-60%. Postviral disorders may affect one or more body systems and markedly reduce the quality of life of recovered patients [1].

The most common clinical manifestations of post-void syndrome include rapid fatigue, dyspnoea, cognitive impairment (complaints of decreased memory and concentration) and sleep disturbance. Many patients also experience psycho-emotional effects of the infection, with studies ranging from 20% to 30% of survivors reporting symptoms of anxiety and depression. Other long-term effects of COVID-19 are also common [8]:

- Headaches and dizziness,
- Muscle and joint pain,
- Hair loss,
- Long-term impairment of the sense of smell and taste,
- Palpitations,
- Episodes of cardiac arrest.

The diversity of symptoms in different patients makes diagnosis difficult and requires a multidisciplinary approach. Proposed mechanisms of post-coronavirus syndrome include direct viral damage to organs (e.g. lung, brain, and heart muscle), immune-mediated effects (autoimmune reactions, chronic inflammation), autonomic nervous system dysfunction, and the effects of hypoxia and coagulopathy observed in severe COVID-19[7].

To date, there are no unified standards for the treatment of post-coronavirus syndrome, and therapy is mainly symptomatic. The management of such patients is a complex task, requiring the participation of specialists from different profiles - internists, pulmonologists, neurologists, cardiologists, psychologists and rehabilitation specialists [2].

The relevance of the present study is due to the high prevalence of PSC and insufficient study of its path physiology.

The aim of the study was to conduct a clinical and functional characterization of postcovical syndrome taking into account multidisciplinary manifestations (respiratory, neurological, psychosomatic, and cardiological) and to evaluate approaches to rehabilitation and treatment of patients with this syndrome.

The present article is aimed at studying the clinical and functional characteristics of post-COVID syndrome, analyzing its pathogenetic basis, as well as systematizing modern approaches to treatment and medical rehabilitation. The presented materials are based on the synthesis of actual domestic and foreign studies, as well as on the generalization of practical experience of observation of patients with long-term consequences of COVID-19.

MATERIALS AND METHODS OF THE STUDY.

A prospective study included 200 patients (108 women and 92 men) aged 18 to 75 years (mean 45 ± 12 years) who had COVID-19 between 2020 and 2021. The diagnosis of COVID-19 was confirmed by PCR and/or a characteristic clinical and radiological picture.

The severity of the disease experienced ranged from mild to severe:

- 100 patients (50%) had a mild course (outpatient treatment),
- 60 (30%) had a moderate to severe course,
- 40 (20%) were severe (requiring hospitalization, with 10 patients (5%) in the intensive care unit and receiving artificial ventilation). Associated pathology was noted in

120 patients (60%), the most frequent being arterial hypertension (30%), coronary heart disease (15%), type 2 diabetes mellitus (10%). Exclusion criteria were: presence of severe cognitive impairment before COVID-19, severe mental illness, terminal oncopathology, and absence of informed consent. All participants signed informed consent; the study was approved by the local ethical committee.

Patients were examined 6 months (26 ± 4 weeks) after COVID-19. Complaints and history were collected, with special attention paid to symptoms persisting since the acute infection or occurring after recovery. Patients completed standardized questionnaires including fatigue intensity (FACIT-F scale or analogue), cognitive status (CFQ - Cognitive Failures Questionnaire for self-assessment of cognitive impairment), and psycho-emotional state - Hospital Anxiety and Depression Scale (HADS) to identify symptoms of anxiety and depressive disorders. General clinical examination was performed: physical examination, measurement of blood pressure, pulse rate, and body mass index.

Spirometry with measurement of forced vital capacity of the lungs (FVCL) and forced expiratory volume in 1 second (FEV1) was performed to assess the respiratory system; lung diffusion capacity (DLCO) was determined by the method of one-stage CO diffusion in some patients. A 6-minute walk test was performed to assess exercise tolerance and distance measurement, as well as to monitor oxygen saturation and heart rate before and after exercise. If indicated, computed tomography (CT) of the chest organs was performed to detect residual changes (fibrosis, 'frosted glass', etc.).

Neurological examination included cognitive function testing (using the Montreal Cognitive Assessment Scale, MoCA) and olfactory assessment (odour identification test if the patient complained of anosmia/hyposmia).

Psychosomatic state was assessed with the involvement of a psychotherapist: the presence of symptoms of post-traumatic stress disorder, anxiety level, depressive symptoms, and sleep disorders were determined (using the sleep quality questionnaire).

To assess the cardiovascular effects of COVID-19, all patients underwent electrocardiographic (ECG) and echocardiography; 24-hour Holter ECG monitoring was performed if they complained of episodes of palpitations or syncope. Laboratory parameters were also analyzed: levels of C-reactive protein, D-dimer, troponin, ferritin, thyroid hormones, glycated hemoglobin - to detect hidden inflammatory, thrombotic, metabolic and endocrine disorders, respectively.

Data are presented as mean and standard deviation ($M \pm \sigma$) for quantitative variables, and as fractions (%) for categorical data. The χ^2 test was used to assess the association between qualitative variables. Differences were considered statistically significant at $p<0.05$.

RESULTS OF THE STUDY AND THEIR RATIONALE.

The study cohort included 200 patients who underwent COVID-19, of whom 55% were female and 45% male. The mean age was 45 years, with 30% of patients being older than 60 years. Table 1 summarizes the main characteristics of the participants, including the severity of COVID-19 and the presence of comorbid pathology.

During the follow-up period 6 months after the acute phase, post-COVID syndrome (presence of at least one clinical symptom or functional abnormality associated with a past coronavirus infection) was diagnosed. The overall prevalence of PCS in the sample was 58% (116 of 200 patients).

The incidence of post-COVID syndrome was correlated with the severity of the disease: mild COVID-19 survivors showed signs of PCS in 40% of cases, moderate COVID-19 survivors in 55%, and severe COVID-19 survivors in 70% ($\chi^2=10.4$; $p=0.005$).

Women were slightly more likely to report prolonged symptoms than men (62% vs 53%, $p=0.12$), but this difference did not reach statistical significance. The mean duration of

symptom persistence was 4.2 ± 1.1 months, with 20% of patients still having symptoms 12 months after illness.

The most frequent symptoms persisting 6 months after COVID-19 were: increased fatigue, dyspnoea on physical exertion, cognitive disorders (difficulty in concentration, memory impairment), sleep disorders, and psychoemotional disorders (anxiety, depressed mood). The frequency of the main symptoms is presented in Figure 1.

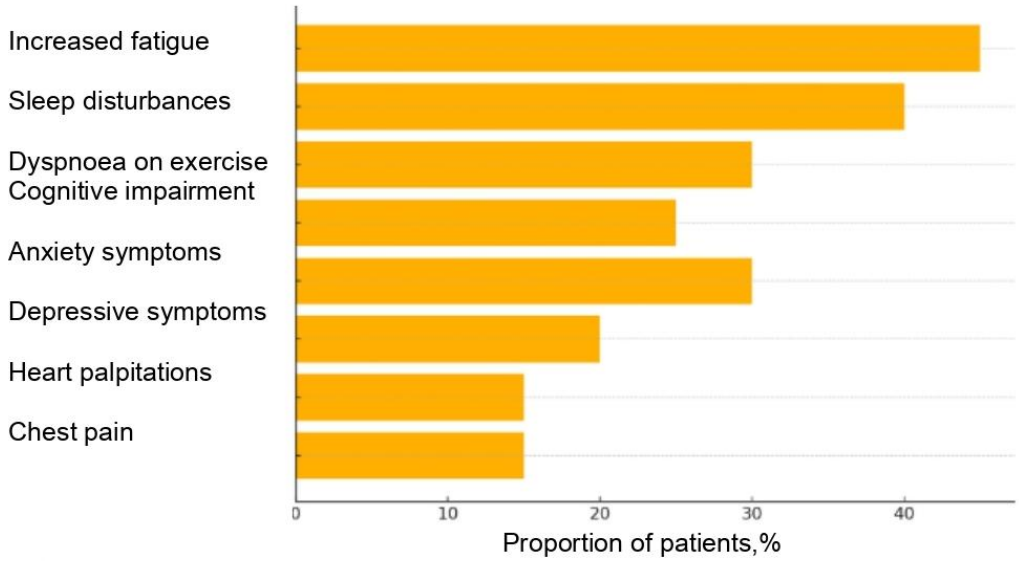

Figure 1. Frequency of the main symptoms of post-COVID syndrome 6 months after COVID-19.

The diagram shows that the most common manifestation was increased fatigue (45% of patients). There was also a high proportion of patients who reported sleep disturbances (40%) and dyspnoea on physical exertion (30%).

Cognitive complaints (difficulty remembering, decreased attention) were present in 25% of subjects. About 30% of patients experienced symptoms of anxiety, and 20% had depressive manifestations. Symptoms such as palpitations (15% of patients reported episodes of palpitations) and persistent chest pain (15%) were relatively less common.

It should be noted that many patients had more than one symptom, reflecting the multiplicity of systems affected in post-coital syndrome.

Table 1. Clinical characteristics of patients included in the study (n=200).

Indicator	Value
Number of patients	200
Age, years (M ± σ)	45 ± 12
Women	110 (55%)
Men	90 (45%)
Mild COVID-19	100 (50%) patients
Moderate COVID-19	60 (30%) patients
Severe COVID-19	40 (20%) patients
Hospitalisation in the acute period	80 (40%) patients
ICU ventilations (severe cases)	10 (5%) patients
≥1 chronic disease before COVID	120 (60%) patients (AH, CHD, DM, etc).

Respiratory symptoms and lung function disorders were among the most frequent and clinically significant components of PCS. Dyspnoea during physical activity persisted in 30% of patients six months after the disease, and in 10% of them it was present even at rest. Chronic cough (mostly dry, episodic), sometimes increasing with exertion or in horizontal position, was observed in 13% of the patients.

Chest pain at the height of inhalation or when coughing was reported by 12-15% of patients; as a rule, these pains were explained by inflammatory changes in the lung tissue and pleura. Spirometry revealed a moderate decrease in the ventilatory capacity of the lungs in some of the respondents: 15% had a decrease in LVEF < 80% of the normal value, 18% had a decrease in PEF1 < 80% of the normal value.

The diffusion capacity was significantly more often impaired: every third patient (33%) had a reduced DLCO (less than 80% of normal values), indicating residual limitations of gas exchange in the lungs. These data are consistent with the results of radiological diagnostics: in 23% of patients, CT of the chest organs revealed residual changes like a 'frosted glass' effect, indicating the preservation of a zone of increased airflow (possibly due to small atelectasis or minimal oedema).

A more serious complication - post-inflammatory pulmonary fibrosis - was diagnosed in 7% of patients (according to CT scan and decreased diffusion indices). These changes led to the fact that about one third (34%) of the patients showed decreased exercise tolerance in the 6-minute walk test: the distance covered was 20% or more less than the age norm, and 10% of the subjects showed a 4% decrease in oxygen saturation from baseline.

Thus, even six months after COVID-19, a significant proportion of patients still had functional respiratory disorders, probably due to diffuse lung damage (viral pneumonia) and associated tissue fibrosis. These results confirm the need for long-term monitoring of the respiratory system of survivors and rehabilitation measures (breathing exercises, pulmonary rehabilitation).

The effect of coronavirus infection on the nervous system was evident in many of the study participants.

Cognitive disorders of varying severity 6 months after the disease were observed in 25% of patients. Most often, patients complained of 'blurred consciousness', difficulty in concentration, slowed thinking and reduced memory for recent events. Objective neuropsychological testing (MoCA) confirmed the presence of mild cognitive impairment in 18% of patients (MoCA total score below the age norm, mainly due to deficits in attention and executive functions). These changes can be regarded as a manifestation of encephalopathy due to COVID-19, and in some cases they resemble the syndrome of moderate cognitive impairment. In addition, 8% of patients continued to experience frequent tension headaches or episodes of dizziness, whereas they had not experienced such complaints before COVID-19.

The mechanisms of neurological complications of COVID-19 are diverse: direct neurotoxic effects of the virus, autoimmune inflammation in the central nervous system, micro vascular thrombosis, and a general decrease in cerebral perfusion during the acute period of the disease have been suggested. After six months, 11% of patients still had partial olfactory impairment - they noted a decrease in the acuity of odour perception (hyposmia) or distortion of odours (parosmia), and this caused significant discomfort in everyday life [4].

This symptom, a characteristic feature of COVID-19, was significantly more frequent in the acute period (in more than half of the patients), but in some of them olfactory disturbances became persistent. The neurological aspects of post-COVID-19 syndrome also include peripheral disorders: about 5% of patients had signs of peripheral neuropathy

(paresthesias in the extremities, reduced reflexes), probably related both to the neurotoxic effect of the virus and to vitamin deficiency (in particular B12) during the recovery period.

Thus, COVID-19 can lead to prolonged nervous system dysfunction, ranging from mild cognitive deficits to sensory impairment, requiring further monitoring and, if necessary, rehabilitation (including cognitive stimulation and vitamin therapy).

Post-COVID syndrome affects not only somatic health, but also the psychological state of patients. In our study, 45% of participants complained of rapid fatigue and general weakness, even in the absence of significant objective abnormalities. This symptom, asthenia, is one of the key components of PCS. Many viral infections (influenza, Epstein-Barr, etc.) have a known syndrome of post infectious chronic fatigue; in COVID-19, such excessive fatigue is often combined with dyspnoea and may have a complex genesis (effects of hypoxia, prolonged bed rest, and immune system dysregulation). Almost half of the patients (40%) reported various sleep disorders: difficulty falling asleep, shallow interrupted sleep, and feeling sleep deprived in the morning. Sleep disturbance exacerbated daytime fatigue and cognitive problems, forming a vicious circle. It should be taken into account that during quarantine and isolation, many people's daily routines shifted and stress levels increased, which could also contribute to insomnia.

The psycho-emotional state of COVID-19 survivors is another important component of the post-COVID syndrome. According to our data, anxiety-depressive disorders were detected in 32% of patients 6 months after the disease. Of these, 22% had clinically significant symptoms of anxiety (HADS-A scale score ≥ 8) and 18% had symptoms of depression (HADS-D ≥ 8) during the follow-up period.

Generalized anxiety disorder was diagnosed in 12% of patients, and 8% had signs of a mild to moderate depressive episode. Post-traumatic stress disorder (PTSD) should be mentioned separately: a severe course of COVID-19, especially associated with hospitalization in the ORIT, invasive ventilatory support, and life-threatening conditions, could lead to the development of PTSD.

In our sample, the clinical criteria of PTSD corresponded to the condition of 5% of patients, with intrusive memories of intensive care, nightmares, avoidant behaviour, and increased anxiety. The presence of pronounced psychological problems in some of the survivors is consistent with the results of foreign studies showing an increased incidence of anxiety and depressive disorders after COVID-19.

Risk factors for psychosomatic complications were previous psychiatric disorders, high levels of stress during the pandemic and long-standing post-coital asthenic syndrome. Identification of psycho-emotional disorders is extremely important, as they negatively affect the overall health recovery and social readaptation of patients. These disorders require correction - including non-medication (psychotherapy) and, if necessary, medication (antidepressants, anxiolytics prescribed by a psychiatrist) [8].

Cardiovascular consequences of COVID-19 were found in patients with previous cardiovascular disease as well as in previously healthy patients. At 6 months after the infection, rhythm disturbances and subjective palpitations were noted in 15% of patients.

According to Holter monitoring data, 10% of patients had resting sinus tachycardia (>90 beats/min on average per day), 8% had episodes of supraventricular tachyarrhythmias (including paroxysms of atrial fibrillation in 2 patients), and 5% had single ventricular extra systoles (Lown gradations 1-2).

The mechanism of palpitations in a part of patients is associated with dysfunction of the autonomic nervous system (sympathetic activation), which is reflected in the diagnosis of postural orthostatic tachycardia syndrome (POTS), developed in about 5% of young patients with PCS.

In addition to arrhythmias, structural and functional changes of the heart were also diagnosed. Echocardiography revealed a moderate decrease in left ventricular ejection fraction (<50%) in 5% of patients, which may correspond to myocarditis or stress-induced cardiomyopathy (Takotsubo syndrome). In 15% of patients, there was evidence of left ventricular diastolic dysfunction (slowed relaxation) without decreased contractility; this change is often associated with hypertension, but in some patients it could be a consequence of myocardial damage in COVID-19.

Elevated levels of cardiac troponin T persisted in 3 patients (1.5%) after 6 months, which may indicate long-term subclinical inflammation in the myocardium. Blood pressure fluctuations were recorded in 20% of patients: episodes of hypertension were followed by normotension, which may be due to dysregulation of the renin-angiotensin-aldosterone system after viral attack on ACE2 receptors. In general, remote cardiac complications of COVID-19 included an increased risk of thrombotic events (one patient was first diagnosed with deep vein thrombosis of the lower leg 4 months after the disease), exacerbation of the course of existing CHD and arterial hypertension, and development of new cases of hypertension (5% of patients were first diagnosed with AH in the postviral period)[10].

Such data are consistent with reports on the involvement of the cardiovascular system in PCS. Undoubtedly, these changes adversely affect the long-term prognosis of survivors, increasing the risk of heart failure and acute vascular accidents, so they require active detection and correction [3].

In the absence of specific methods to eliminate the causes of post-COVID syndrome, treatment is complex and predominantly symptomatic. According to the results of the present study, an individualized rehabilitation and treatment programme was offered to all patients with identified manifestations of PCS.

Drug therapy was prescribed differentially depending on the prevailing symptoms: in case of persisting neurological symptoms (headaches, cognitive impairment) - mild nootropic and metabolic agents (mexidol, piracetam), B vitamins, if necessary - magnesium and sedative phytopreparations; in case of complaints of tachycardia and interruptions - β-blockers in low doses (e.g. bisoprolol 2.5-5 mg) with gradual withdrawal as they improve, as well as anticoagulants in prophylactic doses when indicated (especially in patients with high D-dimer or thromboembolism); in case of signs of ongoing inflammation (elevated CRP, prolonged subfebrile) - short course of non-steroidal anti-inflammatory drugs or low doses of glucocorticoids.

For patients with severe asthenia, metabolic cytoprotectors (e.g., L-carnitine, succinic acid) and multivitamin complexes were prescribed, taking into account possible deficiencies of vitamins D, B12, folate, as well as iron and magnesium. Non-medication rehabilitation is an important component of management.

All patients were recommended a gradual increase in physical activity: first, dosed walks on foot, then performing complexes of respiratory gymnastics and LFK (physical therapy) exercises under the supervision of a rehabilitologist. Moderate aerobic exercise (Nordic walking, swimming, light running) was allowed when the condition improved, while avoiding overexertion was emphasized in order not to provoke a deterioration of well-being.

If respiratory disorders persisted, respiratory muscle training sessions were conducted using breathing machines, stretching exercises and lung drainage exercises.

Psychological support was provided to patients with anxiety-depressive disorders: psychotherapy sessions (in particular, cognitive-behavioral therapy), relaxation training, and stress reduction techniques were conducted. In some cases, pharmacotherapy was prescribed on the recommendation of a psychiatrist (modern antidepressants from the group of SSRIs in low doses, short-course tranquillizers). This multidisciplinary approach - with simultaneous work on somatic and psychiatric aspects - made it possible to achieve improvement: at the

control examination 3 months after the beginning of rehabilitation, 70% of patients showed a decrease in the intensity or complete regression of the main post-coital symptoms.

Special attention was paid to the prevention of post-COVID syndrome. Patients were explained the necessity of vaccination against COVID-19 (if not previously vaccinated) and revaccination according to current recommendations, since vaccinated individuals have a significantly lower risk of both the severe course of COVID-19 and the development of long-term post infection complications [6].

In addition, it is recommended to follow the principles of a healthy lifestyle: a rational diet with a sufficient content of proteins, vitamins and microelements, avoidance of smoking and alcohol abuse, normalization of sleep and physical activity.

CONCLUSIONS.

The present study demonstrates that post-CoVID-19 syndrome is common among COVID-19 survivors and is characterised by multidisciplinary clinical manifestations. Six months after the infection, more than half of the patients have some symptoms or functional abnormalities associated with COVID-19.

The most frequent manifestations of PCS - increased fatigue, dyspnoea on exertion, cognitive impairment and psychoemotional disorders - significantly reduce the quality of life and performance of patients.

Objective examination reveals in some patients persistent changes in the respiratory system (decreased lung function, fibrotic changes), cardiovascular system (rhythm disturbances, signs of myocardial dysfunction), nervous system (cognitive deficit, peripheral neuropathies), which confirms the need for long-term follow-up of the patients.

Risk factors for the development of post-COVID-19 syndrome are a severe course of acute coronavirus infection, the presence of chronic diseases, and female gender. To minimize the long-term consequences of COVID-19, a comprehensive approach to rehabilitation is required: a combination of rational drug therapy (as indicated) with rehabilitation treatment programmes including breathing exercises, gradual physical activity and psychotherapeutic support.

It is equally important to carry out prevention of ‘long-term COVID’ through vaccination of the population and timely treatment of acute forms of the disease.

The developed approaches to the management of patients with post-COVID syndrome require further improvement and study in the framework of larger studies, but it is already evident that multidisciplinary rehabilitation can significantly improve the clinical and functional status and quality of life of individuals facing long-term consequences of COVID-19.

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