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ASTHENIC DISORDERS IN PATIENTS WITH COVID-19

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Asthenic disorders are one of the most urgent and complex problems in the practice of doctors of various specialties. This is due to the high prevalence of asthenia. Up to 50% of patients at an outpatient appointment with a therapist complain of increased weakness, fatigue, and decreased mental performance.

Asthenic syndrome is manifested by increased fatigue, weakness, sleep isturbance, loss of ability to prolonged mental and physical stress, as well as affective symptoms in the form of irritability, frequent mood changes. Patients with asthenic syndrome are characterized by increased excitability, quickly replaced by exhaustion. Asthenia can develop within the framework of chronic fatigue syndrome, also the symptoms of asthenia are basic for various nosologies, preceding or completing the course of the disease. Asthenic disorders can be a manifestation of a wide range of both somatic and mental diseases, in connection with which it is fundamentally important to establish their nosological affiliation. In-depth laboratory and instrumental examination, consultations of specialists (psychiatrist, endocrinologist, etc.), neuropsychological examination are often required to establish the nature of asthenic disorder. It is obvious that the identification of asthenic disorders and the efforts made to correct it do not exclude the need to search for the underlying disease, potentially curable, and combat it.

Clinical manifestations of postcovid syndrome

Despite the fact that acute respiratory disorders and the possibility of their correction are in the focus of COVID-19, an understanding has been formed that many patients who have been ill and no longer have manifestations of acute infectious disease, with negative PCR test results, experience persistent physical, cognitive and psychological disorders.

Initially, postcovid syndrome was considered as a symptom complex that develops during or shortly after COVID-19, lasts more than 12 weeks. and it is not explained by an alternative diagnosis. This term proposed by National Institute for Health and Care Excellence (NICE) UK, included both ongoing symptomatic COVID-19 and post-COVID-19 syndrome. At the end of February 2021, to separate the concepts of "long-term COVID-19" and "postcovid syndrome" by E. Fauci (USA), it was proposed to use a new acronym — PASC (English: post-acute sequelae of SARS-CoV-2 infection/COVID-19 — post-acute consequences of COVID-19). Currently, post-ovoid asthenia is considered as a decrease in physical and/or mental performance as a result of changes in

central, psychological and/or peripheral mechanisms due to COVID-19. At the initiative of Russian therapists, a separate code for the description of postcovid syndrome appeared in ICD-10: U09.9 — The condition after COVID-19. Postcovid asthenia is categorized in ICD-10 as G93.3 — Fatigue syndrome after a viral infection.

The expediency of introducing the concept of postcovid syndrome is due to the wide prevalence of asthenic, cognitive and autonomic disorders in COVID-19 survivors, their significant frequency exceeding that in patients who have suffered other infectious diseases, as well as a significant decrease in the quality of life of patients. After suffering COVID-19, asthenia/ fatigue, inability to concentrate or so-called "brain fog", depression, anxiety, sleep disorders, as well as numerous and diverse vegetative disorders (lability of pulse and blood pressure, orthostatic tachycardia and hypotension, gastrointestinal disorders, dermatological disorders in the form of local hyperemia, itching, sweating disorders, etc., caused, among other things, by mast cell dysfunction). Symptoms occur some time after infection or develop later and persist for several months.

Increased fatigue and a feeling of fatigue are the most common manifestations both acute COVID-19 and its consequences. The most extensive study devoted to the study of the prevalence of symptoms is a long-term COVID-19, is a meta-analysis of 7 studies (47,910 patients aged 17 to 87 years with a follow-up period of 14-110 days), which showed that 80% of patients with COVID-19 retain symptoms after the resolution of acute inflammatory disease. The most frequent are fatigue (58%), headache (44%), attention disorders (27%), hair loss (25%), shortness of breath (24%). Other symptoms are associated with damage to the respiratory system (cough, chest discomfort, sleep apnea, etc.), cardiovascular pathology (arrhythmias, myocarditis), emotional and behavioral disorders (cognitive impairment, depression, anxiety, attention disorder, obsessive-compulsive disorders) and a number of nonspecific manifestations (tinnitus, night sweats, etc.). A study in a cohort of outpatient patients (n=458) showed a high prevalence (73%) of persistent fatigue 4 months after recovery.

Asthenia after a coronavirus infection has been observed before in patients who have had SARS syndrome. For a long period of time, it was manifested by persistent fatigue, diffuse myalgia, weakness, depression and sleep disorders. Since COVID-19 is compared with SARS, it is worth noting that, according to studies, patients who had SARS had persistent asthenia for 1 year from the moment of infection.

Modern ideas about the pathogenesis of postcovid asthenic disorders.

To date, a large number of studies have been conducted to identify markers of damage to neurons and glial cells of the brain, as well as to search for SARS-CoV-2 virus RNA in the cerebrospinal fluid (CSF) and brain tissue of patients who died from COVID-19. In 100 patients with COVID-19 of varying severity, the content of markers such as light chains of neurofilaments in blood plasma was determined, acidic gliofibrillary protein, growth differentiation factor 15, which is a protein from the

superfamily of transforming growth factor-β [24]. The authors found that in the acute stage of the disease, the blood content of all these markers was increased, the increase in their concentration generally corresponded to the severity of the disease. 6 months after the onset of the disease, the content of these markers returned to normal levels, despite the fact that half of the observed patients had persistent neurological disorders in the form of generalized weakness and fatigue, decreased cognitive functions, "brain fog" (difficulty concentrating and decreased mental performance). The authors were unable to establish a relationship between the maximum concentrations of these biomarkers in the acute stage of the disease, on the one hand, and the nature and severity of the manifestations of postcovid syndrome, on the other. The results of the study did not allow the authors to establish a link between the consequences of COVID-19 and the levels of markers of brain damage in the acute stage of the disease, and also there were no signs of a continued pathological process in the substance of the brain in patients with post-cortical disorders.

The results of numerous studies conducted among patients with COVID-19 (patients with various forms of the disease, with or without damage to the nervous system were examined) demonstrated the absence or minimal severity of changes in the CSF characteristic of neurotropic viral infections (pleocytosis, the presence of markers of damage to the blood-brain barrier (BBB)). Similarly in patients with COVID-19, regardless of the presence of neurological and mental disorders and their severity, there is no pathological intrathecal synthesis of immunoglobulins. In the course of individual observations, an increase in the blood content of some markers specific to brain damage was noted, which corresponded to the severity of the clinical neurological manifestations of COVID-19, however, the authors note the ambiguity of the results obtained and their limitations associated with an insufficient number of observations for convincing conclusions. Detection of the virus itself SARS-CoV-2 (its RNA) in CSF is extremely rare, the clinical significance of this phenomenon is relatively small. The results of the vast majority of studies could not confirm the assumption of a high frequency of the specific nature of damage to the nervous system in the acute stage of COVID-19 or in the formation of postcovid disorders.

A possible connection between postcovid neurological disorders and non-neuronal cell damage is discussed. In particular, the possibility of hematogenic infection of endothelial BBB cells, which makes it permeable to a large number of chemicals and blood cells circulating in the blood, or by infecting the leukocytes themselves, used by the virus as a transporter for migration through the BBB. To a certain extent, the assumption of endothelial damage by the SARSCoV-2 virus can explain the high frequency of thrombotic complications of COVID-19, observed, in particular, in the acute stage of the disease. At the same time, according to the results of neuroimaging studies, a significant part of patients with postcovid syndrome have no structural changes in the brain matter, the presence of which could explain the existing

neurological disorders. The role of the glymphatic system of the brain in the pathogenesis of postcovid syndrome, in particular, asthenic disorders, is discussed. Fatigue syndrome after suffering COVID-19 may be the result of difficulty in the outflow of cerebrospinal fluid, leading to stagnation in the glymphatic system with subsequent accumulation of toxic products in the central nervous system.

An inflammatory reaction is also considered as one of the key mechanisms for the development of acute and delayed neurological, mental and autonomic disorders. In patients with COVID-19, there is an increase in the concentration of interleukins (IL) 6, IL-1β, IL-2, IL-8, tumor necrosis factor α (TNF-α) circulating in the blood, leading to systemic immunosuppression, lymphopenia and neutrophilia —key hematological signs of COVID-19. The entry of these molecules into the brain causes an immune response, in particular, in pericytes, macrophages and microglia, which further increases the production of cytokines and probably leads to a violation of cerebral functions

In this regard, the results of a clinical study are of exceptional interest, during which 97 patients with vascular or Alzheimer's dementia with or without systemic inflammatory disease were evaluated for the state of cerebral blood flow, BBB and blood content IL and a number of other markers of inflammation. It turned out, that in the conditions of a systemic inflammatory reaction in patients, an increase in the concentration of IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-13, TNF-α was observed in the blood, which was combined with a regional decrease in cerebral blood flow and a violation of BBB permeability. The degree of these disorders did not depend on the level of beta-amyloid and the nature of dementia. It is likely that the systemic inflammatory reaction in COVID-19 largely determines the nature and severity of existing neurological disorders, including in the long-term period of the disease. As a result of this studies have noted violations of BBB permeability that were not detected in previous studies. It should also be noted that the presence of a systemic inflammatory reaction may be the cause of the development of postcovid syndrome in patients with severe disease, but is not an explanation for the formation of emotional, cognitive and autonomic disorders in patients with mild and moderate COVID-19.

Thus, to date, there is no single theory that can explain the pathogenesis of development postcovid syndrome, but it can be stated with confidence that it is based on a complex of inflammatory, immune reactions in response to acute infectious disease, dysfunctions of neurons, glial cells, cerebral blood flow system and BBB. The severity and duration of these reactions are obviously largely related to the characteristics of the body, in particular, with the reaction to an infectious disease.

Possible approaches to the treatment of patients with postcovid syndrome.

Since the mechanisms of postcovid asthenia and cognitive impairment are not completely clear and only attempts are being made to monitor patients with postcovid syndrome, specific approaches to the treatment of such patients and their rehabilitation are at the stage of formation. Of interest are the results of pilot studies devoted to

evaluating the effectiveness of various medical treatment methods. In particular, encouraging results have been demonstrated with the use of complexes of physiotherapy measures, physical therapy, reflexology, massage, virtual reality.

An increase in the effectiveness of therapeutic and rehabilitation measures can be achieved through optimally selected drug therapy. In this regard, the drug is of considerable interest which has a nootropic and neuroprotective effect, improves cognitive functions, which is due to the modulating effect on brain activity. The results of clinical studies have demonstrated the undoubted effectiveness of the drug in the treatment of patients with acute and chronic disorders of cerebral circulation. As a result of its use, there is an improvement in the state of cognitive functions, a regression of asthenic disorders, which can have a positive effect on the condition of patients with postcovid syndrome.

Conclusion

The effect of SARS-CoV-2 on cognitive activity, as well as on the occurrence of postcovid asthenia, is a serious problem in both elderly and young patients. Lack of data on the pathogenesis of these conditions currently, it reduces the likelihood of prescribing therapy to such patients that could help improve their condition. Since delayed diagnosis can be the main reason for increased cognitive deficits and asthenia, timeliness is crucial to reduce the number of cases of prolonged postcovid syndrome and new cases of dementia. In this regard, an assessment of cognitive functions and asthenic syndrome may be recommended for all patients who have suffered a coronavirus infection, followed by the appointment of optimal therapy.

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