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Long-COVID, neurological and cardiovascular disorders

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Abstract

Introduction. After the disease COVID-19 caused by the SARS-CoV-2 virus, many people recover completely, but others have symptoms that persist for weeks, months or even years after the illness, with the number of patients who are worried about the signs of Long-COVID constantly growing.

The aim. Study of the features of the epidemiological and clinical course, pathophysiological mechanisms of long-COVID development, based on the study and analysis of modern scientific data and the establishment of causal relationships of damage to the nervous and cardiovascular systems.

Materials and methods. The electronic databases Scopus, PubMed, Web of Science, using modern technologies (Obsidian), key terms and words related to Long COVID, distant neurological and cardio-vascular complications have been studied and analyzed.

Conclusions. "Long COVID" is conceptualized as a multiorgan disorder with a wide range of clinical signs that may indicate primarily damage to the nervous and cardiovascular systems. Central or peripheral nervous system lesions occur in more than one-third of patients. Cardiovascular complications, including stroke, are the predominant causes of death of people with "long COVID" (40 %). The most frequent neurological signs of "Long COVID" (>70 %) are fatigue, headache, sleep disorders, emotional disorders and sensorimotor disorders. The processes of neuroinflammatory and oxidative stress predominate in the spread of neurological consequences of "Long COVID".

Keywords: COVID-19; Long-COVID; clinical signs; nervous and cardiovascular systems; cognitive impairment; consequences; health; environment.

Introduction

After the onset of the coronavirus disease (COVID-19) pandemic, it became apparent that the spread of severe acute respiratory syndrome coronavirus (SARS-CoV-2) would have huge implications for health systems and socioeconomic structures around the world. In addition to the excessive number of deaths during the pandemic and the growing number of those who have recovered from COVID-19, the long-term or late consequences of SARS-CoV-2 infection are attracting more and more attention. In fact, the term "Long COVID" was first coined and disseminated through social media by patients who, in the early months of the pandemic, recognized a more complex course of the disease than was described in early reports from Wuhan. Subsequently, related terms, "long-term", "post-COVID" and "post-acute consequences" of SARS-CoV-2, were introduced to refer to persistent symptoms and/or delayed or prolonged complications, in addition to the acute form of COVID-19. Currently, despite the discovery of new variants, after mass vaccination campaigns, in many countries there is a significant decrease in the number of new cases of COVID-19 and hospitalizations [1 - 4].

Prevention of "Long COVID" occupies a very important place in the work of the health care system. However, there is currently only a poor understanding of the main processes associated with the pathogenesis of "Long COVID" syndrome. The WHO has proposed a definition of a clinical case based on the Delphi consensus, according to which "Long COVID" occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months after the onset of COVID-19 with symptoms that last at least 2 months and cannot be explained by other causes or diagnosis [5, 6].

Materials and methods

The electronic databases Scopus, PubMed, Web of Science, using modern technologies (Obsidian), key terms and words related to Long COVID, distant neurological and cardio-vascular complications have been studied and analyzed.

Results and discussion

The main symptoms identified in all "Long COVID" patients were fatigue, shortness of breath, cognitive dysfunction, and others that negatively affect daily life and functioning. They may occur again after recovery, after an acute episode of COVID-19, or persist after an illness, or change or recur over time [7].

Neurological disorders make up one of many aspects of Long COVID syndrome. According to the definitions, the long-term or late neurological consequences of the disease should be distinguished from the well-characterized acute neurological symptoms of SARS-CoV-2 infection. In addition, since "Long COVID" is conceptualized as a multiorgan disease, damage to the central or peripheral nervous system can be detected separately or in combination with pulmonary, cardiovascular, psychiatric, endocrine, hematological diseases [8, 9].

The National Institutes of Health (NIH) associates "Long COVID" with symptoms such as: general weakness or decreased energy that interferes with daily life, fever and chills, sleep disorders, weakness, headache, cognitive impairment, anxiety, and depression, visual, hearing, loss or distorted sense of taste, shortness of breath, chest pain, fainting, muscle pain, joint pain. In addition, recent reports indicate an extremely high prevalence of long-term neurological changes among those who have had COVID-19, with almost a third of patients diagnosed with neurological or psychiatric disorders in the first 6 months after acute illness [10].

Family doctors, infectious disease specialists, neurologists have daily treatment of patients with symptoms of "Long COVID". However, since little evidence has been collected so far, the diagnosis and treatment of neurological complications of "Long COVID" requires more detailed study [11].

Due to the methodological warnings of most of the studies published so far, given the biases in the formation of comparison groups, the lack of a standardized neurological evaluation and the lack of clear differentiation with the symptoms of comorbidities, special care is required when trying to characterize the neurological consequences. Now, the following symptoms have been identified, on the part of the central nervous system (CNS): fatigue, impaired concentration, headache, sleep disorders, cognitive impairment, emotional disorders, dizziness; peripheral nervous system (PNS) – muscle weakness, myalgias,

hyposmia, hypogeusia, hearing loss, tinnitus, sensorimotor disorders (hypesthesia, dysesthesia, tremor) [12 - 14].

In a study involving 1733 people with laboratory-confirmed COVID-19, 76 % of patients 6 months after acute SARS-CoV-2 infection had at least one of the following symptoms: fatigue or muscle weakness (63 %), sleep disturbance (26 %), anosmia or ageusia (11 % and 7 %, respectively), myalgia (2 %) and headache (2 %). Concomitant symptoms of anxiety/depression or pain/discomfort are 23 % and 27 %, respectively [11]. Similar data were obtained because of long-term follow-up of 2433 patients with previous SARS-CoV-2 infection; After a one-year follow-up, neurological symptoms included: fatigue (30 %), myalgia (8 %), dizziness (3 %), headache (2 %) and ageusia / anosmia (1 %) [15]. However, an international online survey of 3762 participants with previous COVID-19 disease indicated a much higher prevalence of neurological symptoms affecting the central nervous system and PNS. In the first 6 months after acute illness, sensorimotor disorders (91 %), cognitive dysfunction (85 %), emotional disorders / mood disorders (88 %), sleep disturbances (79 %), headache (77 %), memory impairment (73 %) and anosmia / ageusia (58 %) were most often reported. It is important that 65 % of patients answered that they had a persistence of neurological symptoms for more than 6 months, and most often it was rapid fatigue (80 %) and cognitive dysfunction (58 %) [16].

According to the results of another study, which involved 165 people who had COVID-19, it was found that during the 6-month follow-up after hospitalization, patients most often reported fatigue, memory / attention loss, sleep disorders and myalgia (70 %). Other symptoms included depression/anxiety (27 %), shortness of breath (21 %), visual impairment (20 %), tingling (19 %), hyposmia/hypogeusia (16 %), urinary dysfunction (14 %), confusion / dizziness (13 %), headache (10 %), instability of posture (9 %) and difficulty swallowing (6 %). The key conclusion of this study was that 40 % of patients had anomalies during the neurological examination that could be objectively determined, with hyposmia (18 %), cognitive deficit (18 %), postural tremor (14 %) being the most common. Thus, these results indicate that objective symptoms of CNS or PNS involvement are observed in more than one-third of patients with "prolonged" COVID [17].

According to the published meta-analysis, which characterized the observation data for 47910 patients, 80 % of people infected with SARS-CoV-2 developed one or more long-term symptoms, with the most frequent being fatigue (58 %), headache (44 %) and attention disorder (27 %). In addition, the following estimates of the prevalence of neurological signs have been reported: ageusia (23 %), anosmia (21 %), memory loss (16 %), hearing loss or

tinnitus (15 %), chills (7 %), dizziness (3 %). It is important that mental disorders, including anxiety and depression, were observed in 13 % and 12 % of patients, respectively, while a lower prevalence was reported for mood disorders, dysphoria, obsessive-compulsive disorder, and post-traumatic stress disorder, each of which affects 2 % of patients [18].

A crucial study to assess the intensity level of neurological and psychiatric illnesses among patients who had COVID-19 over the past 6 months was the release of data from electronic health records 236379 patients. This study proved that the incidence of neurological or psychiatric diagnoses is 34 % within 6 months after SARS-CoV-2 infection, with 13 % of patients receiving such a diagnosis for the first time during this period. In particular, regarding the neurological effects of COVID-19, in terms of predetermined underlying neurological outcomes occurring within 6 months of acute SARS-CoV-2 infection, the authors found that nerve / nerve roots/plexuses (2,9 %) and insomnia (2,7 %), then ischemic stroke (0,8 %), dementia (0,7 %), muscle disease (0,5 %), intracranial hemorrhage (0,3 %), parkinsonism (0,1 %), encephalitis (0,1 %) and Guillain-Barré syndrome (0,1 %) are the most common [11].

In addition to severe respiratory damage, cardiovascular, renal, and gastrointestinal signs, given liver and pancreatic dysfunction, are well characterized by complications of acute COVID-19. The main cardiovascular diseases recorded in the period for 12 months. After infection, there are: cerebrovascular diseases (increased risk of transient ischemic attacks or stroke), arrhythmias (atrial fibrillation, ventricular arrhythmias and atrial flutter), inflammatory heart and pericardial diseases (myocarditis and pericarditis), coronary heart disease (angina pectoris, ischemic cardiomyopathy, myocardial infarction), and other cardiovascular diseases (non-ischemic cardiomyopathy, heart failure, cardiogenic shock, cardiac arrest) [19]. Cardiovascular complications and Long-COVID manifestations are the predominant causes of death of patients with Long-COVID, accounting for about 40 % in its structure [20].

According to the literature, several pathogenetic mechanisms of neurological signs of the acute form of COVID-19 have been identified, including viral neuroinvasion accompanied by aberrant neuroimmunological reactions, endotheliopathy associated with dysfunction of the blood-brain barrier, coagulopathies that accelerate hypoxic-ischemic neuronal damage, metabolic imbalance, oxidative cascade of stress, and cellular apoptosis. However, unlike the acute neurological signs of COVID-19, the biological basis of the neurological effects of "Long COVID" remains poorly understood today. Due to the lack of diagnostic markers and reliable neuropathological data, most published articles currently offer predictable

pathophysiological mechanisms of neurological consequences of "Long COVID", drawing parallels with the pathophysiology of acute COVID-19 [21, 22].

In the acute course of COVID-19, the penetration of SARS-CoV-2 antigens into the central nervous system is facilitated by hematogenous or direct transsynaptic pathways through the involvement of the angiotensin-converting enzyme 2 receptor (ACE2), which is located on the surface of various cell types, considering neurons, endothelial cells and smooth muscle cells of cerebral blood vessels [22]. A cytokine storm induced by SARS-CoV-2 can cause a violation of dense compounds on the endothelial membrane of the blood-brain barrier, which leads to an increase in the permeability of the blood-brain barrier and ensures the transmigration of leukocytes infected with the virus in the central nervous system [23]. In addition, cytokine release accelerates platelet activation and adhesion, causing further endothelial disruption and is associated with increased thrombotic risk seen in the acute course of COVID-19. When cytokines pass the blood-brain barrier, they activate microglial cells, which in turn trigger cascades of apoptosis and demyelination [24]. It is believed that chronic inflammatory and secondary degenerative processes predominate in the spread of neurological "long-term" consequences. In "ACE2-enriched" areas of the brain, considering areas of the somatosensory cortex, direct / orbital gyrus, temporal lobe, hypothalamus / thalamus, brainstem, and cerebellum, PET studies of the brain with fluorodeoxyglucose (F-FDG) in patients with "Long COVID" revealed marked hypometabolism. The decrease in glucose metabolism observed in these areas can be further explained by the processes of oxidative stress, mitochondrial dysfunction, or impaired cerebral autoregulation, which are secondary, in relation to SARS-CoV-2 infection [25].

Another possible mechanism of neurological disorders in COVID-19 is an imbalance in the system of bidirectional interaction between neurocytes and blood capillaries in the central nervous system, which occurs when the endothelium of these capillaries is affected. Changes in capillary - neural interaction can increase the frequency of headaches, confusion, and adverse effects, including stroke mortality in patients with COVID-19. In addition, such violations can cause the development of multiorgan damage in COVID-19 [26].

However, even in patients with severe neurological involvement secondary to acute SARS-CoV-2 infection, SARS-CoV-2 RNA is not often found in CSF or biopsy specimens of patients' brain and skeletal muscles [27, 28]. Since there is currently no evidence that the virus's RNA persists in CSF, the question of whether SARS-CoV-2 cell reservoirs can support chronic infection in the central nervous system or PNS remains open.

In the case-control study, which included 27 patients with previous SARS-CoV-2 infection and 12 healthy people in the control group, heart rate variability dysregulation was significantly associated with COVID-19, as well as with the presence of fatigue in patients with "prolonged" COVID-19. Such data indicate autonomic dysfunction in "Long COVID". In combination with the aforementioned brainstem involvement evidence obtained through neuroimaging studies, these data suggest that the afferent and efferent pathways of the vagus and tongue-pharyngeal nerves are involved in demyelinating degeneration processes secondary to viral invasion [29, 30].

The theory of neuroinflammation in "long COVID" has been confirmed by a series of studies that have confirmed the idea that abnormal humoral and cellular immune responses, markers of systemic inflammation such as interleukin-6 (IL-6), and autoantibodies directed at cellular receptors can be involved in the systemic and neurological effects of "Long COVID" [31]. Regarding neuroinflammatory processes, a study of 56 patients with persistent neurological deficits for more than 6 weeks after coronavirus infection proved a reduced expression of the effector molecule in memory T-cells, which was significantly associated with the severity of cognitive impairment [32].

According to recent studies, despite the persistence of neurological symptoms 6 months after acute COVID-19, a weakening of the intensity of symptoms of CNS damage has been determined. This study involved 100 patients, measured by astrocyte and neuron damage biomarkers, including light chains of neurofilaments (NfL), glial fibrillar acid protein (GFAp), and growth differentiation factor 15 (GDF-15). It was found that despite a significant increase in the concentration of these biomarkers during the acute phase of COVID-19, after 6 months of follow-up, they did not exceed normal values in all patients. However, half of them reported persistent neurological symptoms after 6 months, with fatigue being the most frequent in 40 %, "brain fog" and cognitive changes in 29 % and 25 %, respectively. These findings suggest that CNS involvement may not necessarily be accompanied by neurological outcomes of "Long COVID" and point to the key role of a systematic approach to characterize, differential diagnosis, and treat "Long COVID" symptoms [33, 34].

In addition to the difficulties in differentiating "Long COVID" and exacerbations or the emergence of new, unrelated symptoms, some other aspects should be considered. There is currently no consensus on whether confirmed COVID-19 in the patient's history or serological confirmation of previous SARS-CoV-2 infection should be considered as a prerequisite for diagnosis, as a significant proportion of infected patients with SARS-CoV-2 remain asymptomatic or undiagnosed [35, 36].

Also unresolved is the question of whether neurological outcomes in COVID-19 patients treated in intensive care units (ICU) may fall under "Long COVID." Acute neurological symptoms of COVID-19, including encephalopathy/encephalitis, delirium, cerebrovascular pathologies, epileptic seizures, hypoxic-ischemic brain damage, and neuromuscular disorders, vary considerably in frequency and severity between critically ill patients hospitalized without oxygen support and unhospitalized patients [37, 38]. There is a growing body of evidence to suggest that the long-term neurological deficits of those who survived COVID-19 in the ICU bear many similarities to post-intensive therapy syndrome (PITS) [39, 40].

Regarding the potential risk factors for neurological consequences of "Long COVID", there is currently no reliable data that would allow for the detection of high-risk patients in advance [41]. Currently, there are enough conflicting data on the effect of the severity of the underlying disease on the long-term consequences and neurological signs directly [42]. There are also mixed findings in the literature about the impact of demographic factors on "Long COVID." A number of studies confirm that an increase in age contributes to an increase in the frequency of long-term effects, in other studies it has been found that younger patients may have a higher risk [42, 17]. Also, some scientists suggest a link between the female sex and the neurological symptoms of "Long COVID", others do not find any connection with gender, and some report a higher vulnerability of male patients (by analogy with acute COVID-19) [42 - 44].

Despite the aforementioned limitations in definition and diagnostic approaches, our understanding of the long-term neurological effects of COVID-19 is constantly expanding. Meanwhile, standardized approaches to assessing and reporting on the neurological signs of "Long COVID" syndrome are justified to allow the development of operational case definitions, which will ultimately allow for a better characterization and prevention of the long-term neurological effects of COVID-19.

We are conducting a study among people who have had a history of COVID-19 to identify the connection of promoters of cellular activity with the course of coronavirus infection and their impact on the severity of neurological symptoms in patients with "Long COVID". Based on the study of the features of the epidemiological process, clinical and laboratory changes, it is expected to identify a correlation between changes in the level of biochemical parameters in the acute period of the disease and the development of long-term complications with the involvement of the nervous system, which will allow to develop an algorithm for predicting the development of such complications in patients and convalescents.

Conclusions

Despite the decrease in the incidence of COVID-19, the problem of "Long COVID" is only becoming relevant, as a multiorgan disorder with a significant range of clinical signs that may indicate primarily damage to the nervous and cardiovascular systems. Lesions of the nervous system are observed in more than one-third of patients. Many researchers point to the pathogenetic significance of disorders of the bidirectional interaction of the brain-heart axis in the development of complications with damage to the nervous and cardiovascular systems. Damage to the nervous system leads to disorders of the regulation of the cardiovascular system, which is one of the causes of cardiovascular accidents in patients with "long COVID".

The most frequent neurological signs of "Long COVID" are fatigue (40 – 80 %), "brain fog" (29 %), headache (2 – 77 %), sleep disorders (70 %), cognitive impairment (25 %), emotional disorders (88 %), dizziness (3 – 13 %); muscle weakness (63 %), myalgia (2-70 %), hyposmia, hypogeusia (18 %), hearing loss, tinnitus (15 %), sensorimotor disorders (91 %).

The processes of neuroinflammatory and oxidative stress predominate in the spread of neurological consequences of "long COVID". Pathogenetic mechanisms of viral neuroinvasion accompanied by aberrant neuroimmunological reactions, endotheliopathy associated with dysfunction of the blood-brain barrier, coagulopathies accelerating hypoxic-ischemic neuronal damage, metabolic imbalance, impaired interaction between neurons and blood capillaries of the central nervous system and cellular apoptosis have been studied.

In contrast to the acute neurological signs of COVID-19, the biological basis of the neurological effects of "long COVID-19" remains poorly understood today due to the lack of diagnostic markers and reliable neuropathological data. To confirm the important role of metabolic imbalance, disruption of the oxidative cascade of stress in the development of lesions of the nervous system in Long-COVID, we are conducting a study, the result of which will be the ability to predict the development of such lesions using routine research methods.

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