



Features of Treatment of Neurological Symptoms & Syndromes and Nosological Forms in Persons in the Acute Period of COVID-19 Disease

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Abstract

This scientific article describes various neurological problems faced by patients with coronavirus infection. The article also contains information of a recommendatory nature for the treatment of cognitive disorders. In particular, the effective positive effect of the popular drug citicoline is described. According to various clinical studies, citicoline provides a statistically significant moderate but stable improvement in memory and helps to reduce the severity of behavioral disorders in patients with cognitive disorders of various etiologies.

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1 Introduction

The COVID-19 epidemic originated in Wuhan (China) in December 2019. In general, coronaviruses (Coronaviridae) are a large family of RNA viruses capable of infecting humans and some animals. They were first isolated in 1975. Representatives of this family are coronaviruses MERS-CoV, ARVI-CoV. The latter (SARS-CoV) appeared in 2002 as the causative agent of SARS. This virus is capable of mutating, and all its forms can be potentially dangerous to humans [1]. Survivors of COVID-19 can develop various consequences and complications that last from several weeks to several months after initial recovery, affecting various organs and systems. Various consequences and complications in people who have had COVID-19 can occur not only in adults and the elderly, but also in young people [2]. Currently, a wide range of neurological manifestations of COVID-19 is described in the available literature.

2 Neurological Manifestations of Coronavirus Infection

Neurological manifestations were divided into three categories: related to the central nervous system (dizziness, headache, impaired consciousness, acute vascular diseases of the brain, ataxia, epileptic seizures); peripheral nervous system (problems with taste and olfactory sensations, visual impairment, neuralgia); symptoms of skeletal muscle damage. Due to the risk of infection, mainly subjective symptoms reported by patients and some available examination methods were used to diagnose neurological manifestations. Thus, acute vascular diseases of the brain (ischemic stroke and cerebral hemorrhage) were diagnosed by clinical symptoms and computed tomography of the head [3]. Epileptic seizures were confirmed by the presence of clinical symptoms at the time of examination [4]. Skeletal muscle injuries included cases where the patient experienced pain in skeletal muscles and showed elevated creatine kinase levels in the blood [5].

The effect of coronavirus on the nervous system is most likely caused by penetration through the olfactory and trigeminal nerves and hematogenically through the endothelial cells of the blood-brain barrier (BBB) [6,7]. Immunopathogenesis of disorders of the nervous system in the acute stage of the disease may be due to an excessive immune response - a "cytokine storm", an increase in the permeability of the BBB. Indirect effects of the virus (complications of the disease) by the type of encephalopathy, myopathy, neuropathy of critical conditions can be caused by hypoxia, respiratory and metabolic acidosis, impaired regulation of homeostasis due to organ failure, as well as autoimmune inflammatory and demyelinating processes [8,9].

Angiotensin converting enzyme 2 (ACE2) — a cardiovascular protection factor for various organs, nervous system and skeletal muscles - is also a target for various types of coronaviruses (CoV), including SARS-CoV-2. By binding to ACE2 receptors, viruses can cause an increase in blood pressure — the main risk factor for cancer. Through the vascular system (capillary endothelium), the virus can damage the BBB [10]. It is assumed that in addition to the damage to the central nervous system (CNS) through ACE2 receptors, coronavirus can cause direct damage to neurons in the cardiorespiratory centers of the brain stem. A genetic predisposition to an increased risk of neurological complications associated with SARS-CoV-2 is being considered, partly due to ACE2

polymorphism, but the role of APF2 in the pathogenesis of COVID-19 requires further study [11,12].

Based on currently available data and taking into account evidence of a reduction in mortality from cardiovascular diseases, therapy with APF inhibitors and angiotensin II receptor antagonists should be continued in accordance with current recommendations, regardless of SARS-CoV-2 [13]. A study of the immunopathogenesis of COVID-19 has shown that increased uptake of coronavirus by macrophages can lead to activation of macrophages, secretion of cytokines and other chemokines, since coronavirus-specific T cells and antibodies activate macrophages, which leads to their migration into the central nervous system and, ultimately, to demyelination. Post-infectious neurological complications may be associated with the persistence of coronaviruses in the central nervous system following the stage of acute infection, with subsequent distortion of the body's immune responses, the formation of autoimmune inflammation and demyelination in susceptible people. Putative pathogenic mechanisms include molecular similarity between SARS-CoV 2 and the main myelin protein, as well as direct damage to leukocytes and other immune cells. There is a description of post-infectious encephalitis, Guillain-Barre syndrome, after acute COVID-19 [14]. Secondary (indirect neurological complications) associated with COVID-19 are the result of a violation of the regulation of homeostasis as a result of sepsis, septic shock, pulmonary, renal and hepatic insufficiency, cardiovascular diseases.

Various manifestations of common neurological symptoms of the brain during the course of COVID-19 infection are shown in Figure 1. Neurological symptoms were more common in patients with moderate and severe forms of the disease — 75.7% of patients with concomitant pathology (arterial hypertension, coronary heart disease, diabetes mellitus). A statistically significant relationship between cardiovascular diseases (CVD) and mortality among patients with COVID-19 is shown in the work of Chinese researchers from Wuhan [15]. It was much more difficult for patients with CVD to tolerate COVID 19. It is assumed that cardiotoxicity is associated with pro-inflammatory stimulation ("cytokine storm"), hypercoagulation or direct damage to the myocardium, with the development of myocardial infarction, heart failure and arrhythmia, which, in turn, are important risk factors for stroke [16]. According to experts, highly specific neurological symptoms of COVID-19 in the acute phase of infection include an impaired sense of smell, impaired taste, stroke (ischemic or hemorrhagic), cerebral vein thrombosis [17,18]. The development of COVID-19 is associated with both arterial and venous thrombosis due to coagulopathy due to excessive inflammatory response, platelet activation, endothelial dysfunction and blood stagnation. An increase in the level of D-dimers – markers of hypercoagulation, fibrinogen leads to disturbances in the hemocoagulation system, which correlate with a parallel increase in inflammatory markers and are associated with worse outcomes. Thrombocytopenia was detected in 30-50% of patients [19]. Previous observations conducted in 2013-2014 showed that clinical manifestations of atypical pneumonia contributed to an increased risk of cardiovascular

diseases. This suggests that similar complications may occur in conditions of a new acute respiratory infection [20].

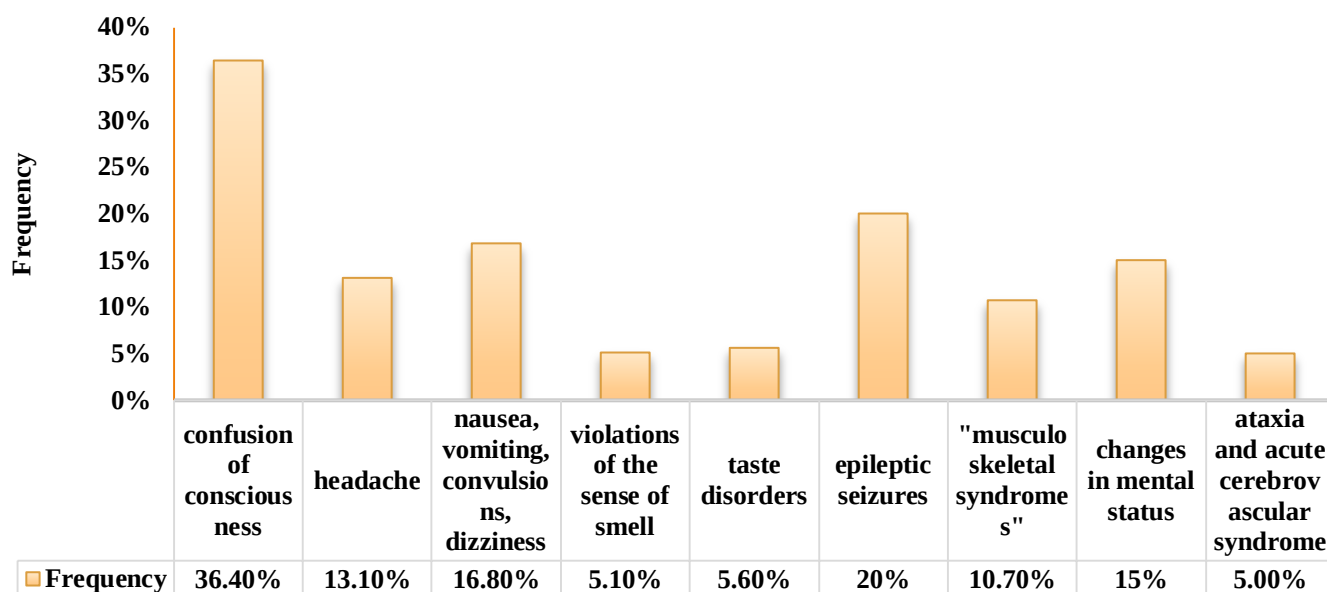


Figure 1: Neurological symptoms of the brain during the course of COVID-19 infection

3 Recovery of Patients after Coronavirus Infection

The recovery of patients with neurological manifestations of coronavirus infection, including stroke survivors, is a new problem. Since humanity has faced this problem for the first time, the medical community has not yet had time to develop specific methods and standards of medical care that allow for the effective and safe restoration of impaired functions in patients with COVID-19 at every stage. Undoubtedly, the system of medical rehabilitation should be comprehensive and include both medicinal and non-medicinal methods [21]. Cognitive rehabilitation is used to restore impaired cognitive functions, including both measures aimed at restoring impaired cognitive functions and improving the cognitive sphere as a whole, and compensatory (adaptive) strategies that allow performing tasks using preserved functions [22]. Therefore, an integrated approach using medicinal and non-medicinal therapies is of great importance.

Treatment of patients should be individual, taking into account pathogenetic factors and aimed at correcting risk factors (smoking, alcohol abuse, low physical activity, obesity), treatment of hypertension, diabetes mellitus and other diseases. One of the directions in the treatment of cognitive disorders is neuroprotection. Neuroprotection is any strategy or combination of strategies that prevents or slows down damage to brain tissues, as well as promotes the restoration of neurons and their environment [23, 24]. It is believed that the use of drugs that contribute to the normalization of metabolism in the brain, having neurotrophic and neuroprotective effects, may be essential in therapeutic tactics [25-32].

Improvement of blood circulation in the system of small vessels of the brain can also be provided with the help of drugs that restore endothelial function (ACE inhibitor with high tissue

specificity-perindopril, statins), drugs that improve microcirculation (for example, pentoxifylline), as well as measures aimed at reducing blood viscosity (smoking cessation, correction of hyperlipidemia or hyperfibrinogenemia). One of the most promising neuroprotectors from the point of view of evidence-based medicine is citicoline, an organic substance belonging to the group of nucleotides-biomolecules. Citicoline restores damaged neuronal membranes, serves as a choline donor for the synthesis of acetylcholine [33]. Citicoline also inhibits the synthesis of phospholipase A2, reducing the accumulation of free fatty acids, restores the functioning of Na⁺/K⁺ - ATPase, increases the activity of antioxidant systems, prevents the processes of oxidative stress and apoptosis, positively affects the cholinergic transmission, modulates dopamine and glutamatergic neurotransmission. In addition, citicoline has a pronounced neuropreparative effect, stimulating the processes of neuro- and angiogenesis [34]. This neurotransmitter also has a neuroprotective effect [35]. Citicoline increases the level of serotonin, which is also supposed to contribute to neuroprotective effects [36]. This reduces the level of glutamate. This neurotransmitter is mainly responsible for brain damage during ischemia due to the action of the N-methyl d-aspartate receptor (NMDA) [37]. Thus, citicoline has neuroprotective properties [35, 37]. According to various clinical studies, citicoline provides a statistically significant moderate but stable improvement in memory, helps to reduce the severity of behavioral disorders in patients with cognitive disorders of various etiologies [38]. Citicoline has been recognized as an effective drug in terms of its effect on cognitive functions. In patients with dementia of various origins, this slowed the progression of the disease during follow-up and improved their daily functioning [39].

One of the citicoline preparations on the Russian market is Noocil. Noocil is available as a ready-made solution for oral use. The indication for the use of the drug is the presence of cognitive and behavioral disorders in degenerative and vascular diseases of the brain. There is evidence of a positive effect of Noocil in vascular diseases of the brain. The drug is recommended to be taken during meals or between meals. The recommended dosage regimen for cognitive and behavioral disorders, degenerative and vascular diseases of the brain is 500-2000 mg per day (5-10 ml 1-2 times a day). The dosage and duration of treatment depend on the severity of the symptoms of the disease.

Rehabilitation is an interdisciplinary intervention aimed at minimizing disability, restoring functional independence and improving the ability to perform daily activities [40]. In particular, with COVID-19, the goals of rehabilitation are to improve functionality, improve the quality of life, promote social reintegration after hospitalization, reduce fatigue, shortness of breath, aging, anosmia and anorexia. Therefore, patients should be offered early rehabilitation measures after discharge in order to minimize the most harmful effects of COVID-19. In the process of rehabilitation, it is necessary to take into account the peculiarities of the disease, taking into account individual needs. Each rehabilitation program should take into account concomitant diseases that may affect clinical progression or the ability to perform daily activities [41]. Given that patients have reported long-term effects of SARS-CoV-2 infection on the central nervous

system even after recovery, indicating the presence of fatigue, loss of concentration and memory, headaches [42], interventions are needed to treat these consequences. It is worth recommending that patients who have undergone COVID-19, especially the elderly, as well as those who complain of fatigue, decreased concentration and memory after discharge from the hospital, use active monitoring for follow-up and prescribe not only medication, but also cognitive behavioral therapy. It is necessary to test for the presence of depression and anxiety in such patients [43,44], as this may reduce the rehabilitation potential.

4 Conclusion

The COVID-19 pandemic has become a serious global problem since December 2019. Despite the most characteristic symptom of respiratory distress, neurological manifestations are also quite often observed in patients with COVID-19. Observations show that cases of damage to the nervous system in COVID-19 are quite common, and neurological disorders can occur both during slaughter in the absence of characteristic symptoms, and after recovery. Neurological disorders associated with COVID-19 had clinical manifestations of damage to various structures of the nervous system — the central nervous system, peripheral nervous system and cranial nerves, as well as mental disorders. Undoubtedly, further in-depth studies of damage to the nervous system in COVID-19 are needed, which will largely complement the information available today.

5 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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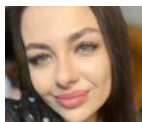
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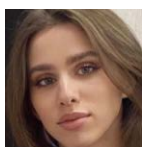
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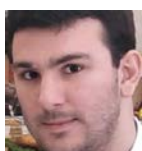
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