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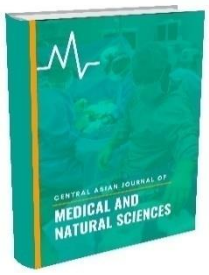

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A Study of Neuropsychological Symptomatology and its Clinical Features in Patients with Covid 19

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Abstract: Coronavirus disease-19 (COVID-19) pandemic continues to grow all over the world. Currently, several research studies have been performed, focusing on the understanding of the acute respiratory syndrome and treatment strategies. However, there is growing evidence of the neurological manifestations in patients with COVID-19. Similarly, the other coronaviruses (CoV) epidemics; severe acute respiratory syndrome (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV) have been associated with neurological complications. CoV neurotropism, direct invasion of the virus to the central nervous system (CNS) and post infection neurological complications were suggested as the cause of these presentations.

Keywords: COVID-19 pandemic, SARS-CoV-2, rehabilitation, recommendations, intracerebral, predominant.

The novel coronavirus infection COVID-19 caused by the SARS-CoV-2 coronavirus poses a global health threat. Neurological disorders found in patients with coronavirus infection have a wide range of clinical signs: headache, dizziness, altered level of consciousness, acute ischemic stroke, intracerebral hemorrhage, venous sinus thrombosis. Evidence suggests that patients with more severe systemic manifestations were more likely to have neurologic symptoms. The main risk factors for the development of ischemic stroke in patients with coronavirus infection are considered. It has been shown that COVID-19 developed more often in people with vascular risk factors, among them there was a higher mortality rate. Various possible and non-mutually exclusive mechanisms are described in detail that may play a role in the development of ischemic stroke in patients with COVID-19, including a hyperinflammatory condition ("cytokine storm"), "coagulopathy associated with COVID-19", disseminated intravascular coagulation. Risk factors for the development of stroke associated with a critical condition in these patients are presented. Stroke, the leading cause of death and disability worldwide, requires immediate treatment and decision-making, as well as 24/7 preparedness for specialized vascular centers. The results of observation of patients with acute cerebrovascular accident in specialized vascular centers for 2 months are presented. before and 15 days after the announcement of quarantine due to COVID-19. The tactics of managing patients with ischemic stroke in conditions of coronavirus infection are considered.

Currently, the world community is faced with a new infectious disease that has not only medical, but also great socio-economic significance - the COVID-19 pandemic (coronavirus disease 2019). Since February 11, 2020, the term COVID-19 has been officially used in the medical lexicon, which was adopted at the level of the World Health Organization (WHO). On the same day, the international committee on the taxonomy of viruses assigned its own name to the causative agent of COVID-19 infection - "SARS-CoV-2" (Severe Acute Respiratory Syndrome Coronavirus 2 / SARS - Severe Acute Respiratory Syndrome associated with Coronavirus [2]. SARS- CoV-2 is a new strain of coronaviruses identified at the end of 2019 and causing a potentially dangerous infectious disease [7].

Coronaviruses belong to the family of RNA viruses that cause infectious disease in some animals and humans. As noted by V.V. Nikiforov et al. (2020), currently 4 types of coronaviruses (HCoV-229E, -OC43, -NL63, -HKU1) circulate among the population all year round [2]. They cause damage to the upper respiratory tract of varying severity. As a rule, diseases caused by the coronavirus family are mild, without severe symptoms [2]. According to the International Committee on the Taxonomy of Viruses, the coronavirus family includes 40 types of RNA viruses and is divided into two subfamilies [5]. A complete viral particle has a size of 80-220 nm [2.5]. Various studies show that the envelope of the coronavirus consists of a lipid membrane, glycoprotein projections (peplomer), membrane glycoprotein, small envelope glycoprotein, and hemagglutinin esterase [5]. Large spiny processes, i.e. peplomeres of the virus in the form of a club, resembling a crown [2]. The persistence of the coronavirus in the environment is variable. Thus, in aerosols the virus is stable for three hours, on plastic surfaces - up to three days and on cardboard - 24 hours. There is evidence that under certain conditions (moderate ambient temperature) the virus is stable up to 17 days [7, 2 , 20], and remains on the outer surface of the mask for more than seven days. According to other sources, the SARS-CoV-2 virus has low resistance in the external environment [2]. Thus, the virus dies under the influence of disinfectants, heating to 40 ° C for 1 hour and up to 56 ° C in 30 minutes [2].

Pathogenesis. The main routes of transmission of coronavirus are airborne, airborne dust and contact. The fecal-oral route of transmission of the virus is not excluded. Transmission from diseased individuals or asymptomatic carriers of the virus is also possible [7]. The spines of the coronavirus are associated with a specific mechanism of its penetration through the cell membrane by imitating the molecules to which the transmembrane receptors of the cells respond [2]. Researchers report that the SARSCoV-2 coronavirus is believed to be a recombinant virus between the bat coronavirus and another, unknown in origin, coronavirus [2, 20]. Susceptibility to the virus is high in all population groups. However, the risk groups for the severe course of coronavirus infection and the risk of death include persons over 60 years of age, as well as patients with comorbid pathologies. The pathogenesis of SARS-CoV-2 is being actively studied [5]. It is believed that the main target cells for coronaviruses are cells of the alveolar epithelium [2]. It is important to note that in an adult, the number of alveoli is 600 - 700 million. The diameter of one alveolus of an adult is 280 microns, in old age it reaches 300 - 350 microns. The total surface area of the alveoli can vary from 40 m2 during exhalation, to 120 m2 during inhalation. According to modern data, the inner layer of the alveolar wall is formed by respiratory alveocytes (type 1 alveocytes), large (secretory) alveocytes (type 2 alveocytes) and alveolar macrophages (type 3 alveocytes). Type 1 alveolocytes involved in gas exchange occupy a much larger area (97.5% of the inner surface of the alveolus) compared to type 2 alveocytes (granular, cuboid, secretory cells). Like type 1 alveocytes, type 2 alveolocytes are located on the basement membrane and produce surfactant, a surfactant that lines the inside of the alveoli and prevents them from collapsing [6]. Thus, alveolocytes of all types form the alveolar epithelium, in the cytoplasm of which the replication of the coronavirus occurs.

When discussing the pathogenesis of coronavirus infection, it is important to note that normally the surfactant is constantly renewed due to phagocytosis by alveolar macrophages (type 3 alveocytes) and

its synthesis by type 2 alveolocytes. In addition to the collapse of the alveoli, surfactant prevents foaming. The regulation of surfactant secretion involves catecholamines, estrogens, thyroxine, glucocorticoids, which increase the production of surfactant [6]. At the same time, insulin, androgens, and atropine inhibit surfactant production. It should be noted that a decrease in surfactant production is observed with chronic hypoxia, with damage to type 2 alveolocytes, with inhalation of tobacco smoke, pure oxygen, etc. In this case, gas diffusion is disturbed, atelectasis and pulmonary edema develop, and foam is formed [6].

In the cells of the alveolar epithelium, after assembly of virions, they pass into cytoplasmic vacuoles, which migrate to the cell membrane and, by exocytosis, exit into the intercellular space [2]. The formation of syncytium (from the Greek syn - together and kytos - a receptacle, here - a cell) under the influence of a virus makes it possible for the latter to quickly spread into tissue. Further, the virus causes an increase in the permeability of cell membranes and increased transport of albumin-rich fluid into the interstitial tissue of the lung and the lumen of the alveoli [12]. It will be appropriate to note here that proteins and lipids of a surfactant inhibit its synthesis. On the other hand, under the influence of the virus, progressive damage to type 2 alveolocytes is accompanied by inhibition of surfactant synthesis. Consequently, collapse of the alveoli and impaired gas exchange occurs with the development of acute respiratory distress syndrome (ARDS). In turn, this additionally supports the development of hypoxemia, vasoconstriction of blood vessels and hypoperfusion of the lungs [6]. In parallel, inactivation of the alveolar surfactant occurs and a further deterioration in the expansion of the lung tissue. Thus, systemic hypoxemia develops - a decrease in the oxygen content of less than 90-88%.

Infection of the host cell occurs through the exopeptidase of the angiotensin-converting enzyme receptor 2 [7]. Expression of this receptor was detected not only in type 2 alveolocytes, but also in cardiomyocytes, epithelial cells of the kidney, intestine, and vascular endothelium [7]. Perhaps this is another path leading to multiple organ damage and the associated risk of adverse outcomes in COVID-19 [11]. The spread of the virus to all organs leads to microvascular damage due to hypoperfusion, increased vascular permeability, vasospasm, direct damaging effect of the virus on the vascular endothelium of the glomerular apparatus of the kidneys and the brain [7]. It is believed that the coronavirus can cause direct damage to the kidney structure. The role of the expression of angiotensin-converting enzyme and dipeptidyl peptidase-4 in renal tubules is discussed [7]. This is confirmed by the detection of viral RNA in kidney tissue and urine during coronavirus infections [8], including SARS-CoV2 [1].

The European Stroke Organization (ESO) recently issued a press release warning of a possible increased risk of death or disability from stroke during the COVID-192 pandemic. This press release concluded that the lack of optimal care is likely to lead to a greater risk of death and a lower likelihood of full recovery. ESO also noted that stroke patients should continue to be admitted to hospital as soon as possible and that efforts should be made to maintain routine levels of stroke management, including intravenous and endovascular reperfusion strategies, regardless of the patient's COVID-19 status, to avoid unnecessary “Collateral damage” due to inadequate treatment of this often disabling or life-threatening condition. The American Heart Association and the American Stroke Association (AHA / ASA) have provided interim guidance for stroke centers during the current crisis.

Infection with severe acute respiratory syndrome caused by the SARS-CoV-2 coronavirus leads to the coronavirus disease COVID-19 in an unknown percentage of people and is a serious psychological stressor in addition to its enormous impact on all aspects of people's lives. But beyond the psychological stress associated with the pandemic, the direct effects of the virus itself and the subsequent immunological response of the host to the human central nervous system and related results are unknown. We review the currently available evidence of neuropsychiatric consequences

associated with COVID-19 [1]. If we draw a parallel with past outcomes associated with a viral pandemic, we can see that different types of neuropsychiatric symptoms, such as encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes, can accompany an acute viral infection or can follow infection. after a few weeks, months or longer in recovered patients [2].

There are already reports of acute CNS-related symptoms in people affected by COVID-19 [3, 4]. Evidence for acute neuropsychiatric symptoms in COVID-19 cases is emerging. An initial report of 217 hospitalized patients in Wuhan, China described neurological manifestations in nearly half of patients with severe infections (40 of 88), including cerebrovascular complications (eg, stroke), encephalopathy, and muscle injuries [5].

SARS-CoV-2 is a virus genetically similar to other human coronaviruses that cause severe illness in humans [6]. The genetic similarity between SARS-CoV-2 and SARS-CoV (the causative agent of SARS) has been reported to be 79.5% [7]. It has been shown that SARS-CoV and SARS-CoV-2 bind to angiotensin converting enzyme 2 (ACE 2) as a cell entry receptor to enter human cells. New evidence suggests that the CoV spike glycoprotein (s) that binds SARS to the cell membrane is longer in SARS-CoV-2 and therefore can bind SARS-CoV-2 with a higher affinity for the ACE 2 receptor. This has been proposed to explain the increased infectivity of SARS-CoV-2 and is thought to contribute to a higher neuroinvasive potential than previous CoV viruses [8]. This is especially important given the widespread expression of ACE 2 in the brain, which suggests that SARS-CoV-2 could potentially infect neurons and glial cells throughout the CNS. As of May 2020, 34% of patients admitted to hospital for COVID-19 disease are known to have neurological symptoms compared to sporadic case reports with SARS-CoV [9]. However, the extent to which neurological symptoms reflect the neuroinvasive and neurovirulent effects of the virus or are secondary to hospitalization-related treatment remains unclear.

A retrospective report on patients with COVID-19 from Wuhan describes encephalopathy or persistent (more than 24 hours) changes in consciousness in about a fifth of the people who died from this disease [10]. Given the emerging evidence of hypercytokinemia in hospitalized COVID-19 patients [11], the burden of long-term delirium following SARS-CoV-2 may be significant, especially for older patients who are more susceptible to post-infectious neurocognitive complications.

Depression and anxiety have been shown to be associated with outbreaks of CoV [12], but it remains unclear whether the risks are associated with viral infections as such or with the host's immune response. There are data from studies of a series of COVID-19 cases, which show that these patients may have various neurocognitive disorders associated with the disease or its treatment, including stroke of large vessels, hypoxic brain damage, encephalopathy, encephalitis, acute disseminated encephalomyelitis [13].

With the ever-growing number of reports of neurological complications caused by COVID-19, it can be argued that a significant number of patients will need neuropsychological care in the coming months and years, which requires clear clinical care using evidence-based medicine data. In the field of clinical practice, the main problems of the use of evidence-based medicine are associated with the unclear criteria for identifying the norm and pathology of mental activity. Particular difficulties in deciding on the presence of a particular mental pathology arise in the case of the study of individuals in a general, non-selective in terms of traditional psychiatric contingents, population. In this case, clinical specialists are faced with both minimal signs of a clinically delineated mental pathology, and with the usual everyday complaints that are present in every practically healthy person. From the standpoint of evidence-based medicine, the main task in distinguishing between mental norm and pathology is to separate the clinical cases requiring intervention from those that are due to individual personal characteristics and do not therefore require any supervision or specialist consultation [1].

However, in everyday clinical practice, most of the distributions of variables reflecting indicators of mental and personality functioning cannot be easily divided into “norm” and “pathology”, since these distributions do not have distinct breaks or two different peaks, one of which would correspond to a normal result, and the other - pathological. From the point of view of the evidence-based approach, the division of populations into "mentally healthy" and "mentally ill" seems impossible for at least two reasons. Firstly, many mental illnesses proceed latently, have their own period of development, manifesting themselves as a gradual transition as dysfunction increases from low values to the study and healthy, and patients actually belong to two different populations, it is almost impossible to recognize each of them in the general population, since in different patients the same indicator, in contrast to the indicators in patients with somatic diseases, can take on different values, overlapping the values of this indicator in healthy people [13].

It has now been clearly established that some patients with COVID-19 develop severe neurological complications, such as infectious toxic encephalopathy, viral encephalitis and stroke. Neurological and neuropsychological symptoms can also occur with atypical acute respiratory distress syndrome. Many patients with severe COVID-19 have had to be monitored in an intensive care unit, further increasing the likelihood that these people may develop neuropsychological dysfunction during hospitalization and in the months and years after discharge [13]. The associated psychiatric symptoms experienced by such patients exacerbate these problems [10]. As such, neuropsychologists now have an important role to play in evaluating and treating COVID survivors.

In addition, the cause of neuropsychological disorders may be the ability of the virus to cause coagulopathy, thrombosis and inflammation [13] against the background of atypical acute respiratory distress syndrome [11]. Studies have shown that individuals after suffering from respiratory distress syndrome have a deficit in memory, attention, fluency, information processing speed and executive functions, while 30 to 80% of patients continue to show cognitive impairment one year after atypical acute respiratory distress syndrome [12].

Conclusion. In this review, we tried to gather and summarize the results of all the studies reporting neurological disorders observed in patients with CoV infections. However, in some of the reported patients, the neurological manifestations might not be associated with the CoV infections and just coincidentally occurred due to the patient’s underlying comorbidities. Moreover, in patients with severe CoV infections, the associated sepsis and organs failure my lead to different neurological presentations which can be seen in any of critical conditions. In addi- tion, in several studies, particularly in the case of COVID-19, sufficient investigations have not been performed and hard to believe that the neurological manifestation was related to CoV infection. Finally, yet importantly, the neurological symptoms in some of these patients might be medications side effects given CoV infected patients have been treated with different classes of medications, which have side effects,not necessarily reported in the studies.

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