Review article

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COVID-19: infection and neurological complications

Mykola I. Lisianiy, Eugene G. Pedachenko

Department of Neuroimmunology, Romodanov Neurosurgery Institute, Kyiv, Ukraine

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Address for correspondence:
Mykola I. Lisianiy, Department of Neuroimmunology, Romodanov Neurosurgery Institute, 32 Platona Mayborody st., Kyiv, Ukraine, 04050, e-mail: nimun.neuro@gmail.com

The issues of neurological complications after coronavirus disease 2019 (COVID-19) are highlighted, since coronaviruses affect not only the respiratory system but also other organs and systems of the body, notably they can cause neurological disorders and diseases. There is little evidence for a direct mechanism of SARS-CoV-2 virus neuroinvasiveness and neurotoxicity. Various mechanisms of coronavirus invasion into the brain are discussed - anterograde and retrograde, neuronal spread, transcriptional and hematogenous pathways. Retrograde / anterograde transport and transsynaptic transmission of the virus have been confirmed by *in vitro* studies, notably SARS-CoV-2 can enter the central nervous system through olfactory nerve receptor cells. Once in the olfactory bulb, the coronavirus can spread to the cortex and other brain structures, in particular the hippocampus and spinal cord. Invasion of the virus into the central nervous system is also possible by spreading along peripheral nerves, such as along the vagus nerve, which innervates the lungs and intestines. The virus invasion into the central nervous system through the blood-brain barrier is considered to be one of the most frequent routes. There are several possible mechanisms for the spread of SARS-CoV-2 across the blood-brain barrier (circulation of viral particles in the bloodstream, viral transcytosis through vascular and capillary endothelial cells, infection of leukocytes with viruses and their transmission of viruses across the blood-brain barrier ("Trojan horse")). However, there is no robust evidence of CNS infection with SARS-CoV-2. Hypoxia induced by the cytokine storm and respiratory distress lead to the impairment of brain metabolism and neurological complications development. There is an ongoing debate as to whether neurological disorders are primary neurological symptoms or secondary consequences of acute respiratory distress syndrome and inflammation.

Among the large number of disorders of the nervous system, there are five main types with long-term neurological complications associated with COVID-19: 1) encephalopathy with delirium / psychosis, 2) inflammatory syndromes of the central nervous system, including encephalitis, myelitis, acute disseminated encephalomyelitis, 3) ischemic strokes (half of them with pulmonary embolism), 4) peripheral neuropathies, Guillain-Barré syndrome and brachial plexopathies, 5) other disorders of the central nervous system.

Incompleteness or inconsistency of statistical data on neurological complications after infection was noted. Further study is required of all early and long-term manifestations of neurological disorders and diseases in mild and asymptomatic manifestations of infection, acute and long COVID-19 and after vaccination.

Keywords: *COVID-19; SARS-CoV-2 virus; neurotoxicity; neurological complications*

The SARS-CoV-2 virus is known to be a member of the human coronavirus family. Of the 7 viruses, 4 (NL63-CoV, HKU1-CoV, 229E-CoV and OC43-CoV) usually cause cold symptoms ("cold viruses"), while SARS-CoV, MERS-CoV and SARS-CoV-2 cause pandemics (SARS - in 2002 and 2003, MERS - in 2012). The 2019 coronavirus infection pandemic (COVID-19) is associated with SARS-CoV-2 virus [1].

SARS-CoV-2 is the β-coronavirus that has about 80% of amino acid sequences identical to those of SARS-CoV, and 50% of amino acid sequences identical to those of MERS-CoV [2]. Like SARS-CoV, SARS-CoV-2 binds to the enzymatic domain of the angiotensin-converting enzyme-2 receptor (ACE-2), present on the surface of many body cell types (alveolar cells, intestinal epithelial cells, vascular and renal endothelial cells, immune cells (monocytes / macrophages, lymphocytes), neuroepithelial cells and neurons) [3,4]. After binding of the virus spike protein (S) to the ACE-2 receptor, the virus enters the cell, the mechanism of which has not

been definitively elucidated [5–7]. SARS-CoV-2, despite being similar to other covid viruses, demonstrates differences due to their high binding affinity to the ACE-2 receptor [8]. SARS-CoV-2 S-protein is thought to be more positively charged than SARS-CoV, and the ACE-2 binding interface has a negative electrostatic potential. The electrostatic difference provides a stronger interaction between these proteins [9,10]. It is likely that increased S-protein binding affinity may lead to higher virulence of SARS-CoV-2 [11,12].

It is known that coronaviruses do not always affect only the respiratory system. They can also affect the central nervous system (CNS), leading to neurological damage and diseases. There is no evidence of a direct mechanism of neuroinvasiveness and neurotoxicity of SARS-CoV-2 [13]. In addition to systemic symptoms of the disease, such as cough, fever, respiratory complications, patients may have neurological disorders (headache, dizziness, hyposmia, myalgia, ataxia and convulsions) [14,15]. There are a large number of reports of cerebral edema, partial neurodegeneration and encephalitis in severe cases of COVID-19 [13,16,17]. Neuroinvasive ability has been demonstrated for most β-coronaviruses (SARS-CoV [20], MERS-CoV [21], 229E-CoV [22], OC43-CoV [23] and HEV [24]). Although the mechanisms of SARS-CoV-2 neuroinvasion have not been definitively elucidated, given the high similarity of viruses and common routes of infection (e.g., SARS-CoV), a similar route of virus entry into the brain may be characteristic of SARS-CoV-2. [19]. In the case of SARS-CoV-2 infection, hyposmia is one of the common symptoms [16] indicating olfactory dysfunction, probably due to infection of neuronal and non-neuronal cells in the olfactory system as well as cranial nerves [26,27]. Various mechanisms of coronavirus invasion into the brain are suggested, including anterograde and retrograde, neuronal spread, transcriptional [8,16,19,28] and hematogenous [29] pathways. Retrograde/ anterograde transport and transsynaptic transmission of the virus have been confirmed by *in vitro* studies in which SARS-CoV-2 was detected in neuronal soma and neurites using human brain organoids [27]. SARS-CoV-2 can enter the CNS through olfactory receptor cells, passing through the cribiform plate, contacting the second-order neurons of spherical glomeruli [28]. The passage of the virus along the olfactory nerve through the cribiform plate is called the "transcriptional pathway". Once in the olfactory bulb, the coronavirus can spread to the cortex and other brain structures, including the hippocampus and spinal cord [23]. It is also assumed that the virus can enter the CNS, spreading to peripheral nerves, for example, along the vagus nerve, which innervates the lungs and intestines [28]. There is no direct evidence for spread of SARS-CoV-2 along the vagus nerve. Further research should be carried out in this direction.

A hematogenous route of virus entry into the brain is widely discussed. The blood-brain barrier (BBB) is one of the most common routes for viruses to enter the CNS [58]. There are several possible mechanisms for the spread of SARS-CoV-2 through BBB: the circulation of viral particles in the bloodstream [25,29], viral transcytosis through vascular and capillary endothelial cells, infection of leukocytes with viruses and transmission of viruses through the BBB - a well-described mechanism "Trojan horse" [31] and is characteristic for many other viruses. Once in the blood vessels, the virus enters the brain, and inside the microvessels, viral S-protein and the ACE-2 receptor on the capillary endothelium are bound, leading to virus transmission through the basolateral membrane [8,32]. Structural analysis showed that virus-like particles actively pass through endothelial cells of brain capillaries, suggesting that the hematogenous route is the most likely route of SARS-CoV-2 invasion [4]. In addition, SARS-CoV-2 causes a systemic inflammatory response and cytokine storm, which is accompanied by a significant disruption of BBB permeability [30,33]. Disruption of the barrier can lead to both virus permeability and infection of immune cells, which leads to an increase in the inflammatory response [34]. Possible infection of peripheral lymphocytes and macrophages with the virus allows them to be used as a means of spreading the infection, facilitating passage through the BBB into the meninges and vascular plexus [30,35]. One noteworthy claim, that the ability to infect leukocytes (mainly monocytes / macrophages) is also characteristic of other coronaviruses, namely 229E-CoV and SARS-CoV [36,37]. The "Trojan horse" mechanism usually suggests the extravasation of infected leukocytes into the meninges and cerebrospinal fluid [38]. However, there is no robust evidence of SARS-CoV-2 immune cell infection.

Hypoxia induced by a cytokine storm and respiratory distress lead to impaired brain metabolism and the development of neurological complications [29]. There is debate as to whether neurological disorders are primary neurological symptoms or secondary consequences of acute respiratory distress syndrome. Most often, neurological symptoms are predominantly nonspecific and short-lived (loss of smell and taste, headache, malaise, myalgia and dizziness). In moderate and severe cases, acute cerebrovascular disorders (strokes), impairment of consciousness, skeletal muscle damage occur. [39,40]. These early manifestations can be considered as a direct effect of the virus on the CNS [19, 41]. Unfortunately, recovery from an acute infection does not always mean the complete disappearance of the virus. If the infection becomes chronic, it can lead to long-term consequences, in particular, chronic neurological disorders and disease [29]. Some authors report the persistence of coronaviruses in the CNS and other body tissues [39]. Thus, MHV-CoV RNA was detected in the brain of mice even 10–12 months after infection. Chronic demyelination of the CNS persists for 90 days after infection with the virus, and the virus is detected in demyelinated axons 16 months after infection [43]. These experimental studies are confirmed by clinical observations. Thus, the neurotropic viral infection led to an exacerbation of the inflammatory response in the brain, leading to encephalitis or an autoimmune reaction (i.e., demyelination) in patients with COVID-19 [26,30]. There are publications of cases of Guillain-Barré and Miller-Fischer syndromes without detection of SARS-CoV-2 in spinal cord samples, which confirms the role of inflammatory and autoimmune response in neurological manifestations [44,45]. Regardless of whether the impairment of the immune response persists after the end of the disease and the release of the body from the virus, neurological

disorders can develop, including dementia, depression, and anxiety [46]. Although a direct link between SARS-CoV-2 and cognitive impairment has not been unequivocally proven, viral neurotropism and the long-term neurological manifestations described confirm this possible relevance. Thus, complaints of cognitive impairment have been reported following SARS-CoV-2 infection, particularly 10–35 days after discharge from hospital [41]. A number of cohort studies have reported changes in neurological and mental status, such as the development of encephalopathy, encephalitis, psychosis in patients aged 23 to 94 years, which predominated in elderly patients [48]. It is still not clear whether the neurological symptoms of COVID-19 are the result of neuroinflammation caused by a cytokine storm and immune disorders, or selective viral damage to parts of the brain. However, these CNS damage and immune system disorders can significantly affect the long-term neurological consequences, in particular, the development of neuropsychiatric disorders.

There is an increasing number of publications on neurological disorders in COVID-19. Therefore, it is impossible to provide accurate statistical data on the nature and frequency of these complications. Many publications are controversial due to the small number of observations and incomplete examination of patients. In 2021, a meta-analysis of data from 44 articles on neurological complications after infection was performed, analyzing a sample of 13,480 patients of all ages with a different clinical course of COVID-19. The mean age of patients was 50.3 years. Of the neurological complications, myalgia (22.2%), taste perversion (19.6%), olfactory disturbance (18.3%), headache (12.1%), dizziness (11.3%), encephalopathy or cognitive dysfunction (9.4%), ataxia or movement disorders (2.1%). About 2.5% of patients with COVID-19 suffered from acute cerebrovascular disease (ischemic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis). One third of patients (31.1%) were seriously injured, of whom 20.6% were hospitalized in the intensive care unit. About 37.4% of patients had concomitant pathology, 5.7% - had a neurological disease before infection. Muscle pain and clinically significant muscle damage, as evidenced by elevated levels of creatine kinase and lactate dehydrogenase, occupied the first place among the complications in severe course of the disease. This may be due to the direct effect of the virus on skeletal muscles expressing the ACE-2 receptor [50,51], or a mediated response to an inflammatory response system identified by a cytokine storm and muscle tissue damage [52-55]. It is assumed that the occurrence of anosmia in patients with COVID-19 is associated with a high expression of genes responsible for the invasion of SARS-CoV-2 on the epithelial cells of the nasal mucosa [51]. These findings may explain why taste and smell disorders may sometimes be the only signs or very early symptoms of COVID-19 [51,52]. Although other explanations are possible, such as edema, impaired mucous microcirculation, nerve signal transmission block, and so on. The increased risk of ischemic stroke and venous sinus thrombosis [56] is explained by various mechanisms - hypercoagulation [57,58], high systemic inflammatory response, cytokine storm, vascular endothelial damage [59], heart disorder leading to cerebral embolism [60]. The pathophysiological mechanisms underlying cerebrovascular events in COVID-19 need further study. There is a biological rationale for vasculopathy with SARS-CoV-2 damage to the endothelium of the vascularature of the brain and the whole body, reminiscent of cerebrovascular events such as coagulopathy, characteristic of stroke in sepsis [49]. To prove this, comprehensive studies with control groups (patients hospitalized with COVID-19 but without cerebrovascular disorders and patients with cerebrovascular disorders without COVID-19) should be performed.

Among a large number of disorders of the nervous system, there are five main types of long-term neurological complications associated with COVID-19: 1) encephalopathy with delirium / psychosis in the absence of characteristic changes on magnetic resonance imaging or cerebrospinal fluid, 2) inflammatory syndromes of the central nervous system, in particular encephalitis, myelitis, acute disseminated encephalomyelitis, which is often hemorrhagic, 3) ischemic strokes (half of them with pulmonary embolism), 4) peripheral neuropathies, including Guillain-Barré syndrome and brachial plexopathies, 5) other disorders of the central nervous system [62]. There are also indications that neurological disorders may occur before the classic signs of COVID-19, such as fever, cough, nasal congestion, so timely diagnosis is required, taking into account the possible neurological manifestations of COVID-19.

A review of 42 publications (late 2019 - early 2020) identified 82 cases of COVID-19 with serious neurological complications [63]. All patients had positive results of polymerase chain reaction of nasopharyngeal swabs for the presence of SARS-CoV-2, two patients - cerebrospinal fluid. Cerebrovascular strokes were detected in 40 (48.8%) patients, neuromuscular disorders in 23 (28.0%), and CNS complications related to infection or inflammation of the brain in 19 (23.0%) patients. Consequences of diseases were different: 27 (32.9%) patients recovered, 15 (18.3%) had good results, 21 (25.6%) had poor results, and 15 (18.3%) died. Thus, in more than 40.0% of patients the results of treatment of neurological complications were unsatisfactory. The long-term effects of COVID-19-related damage and / or nervous system dysfunction are unknown. Some reports [45,46] describe persistent symptoms of the disease several months after the infection has disappeared, including smell and / or taste disorders, chronic fatigue, and impaired recognition. Long-term complications of infection are referred to as "post-acute" sequelae of COVID-19 (PASC), or Long COVID. There is little direct evidence of such complications. Similar neurological disorders are observed in other viral infections that cause neurological diseases (human immunodeficiency virus, West Nile virus, herpes and picornaviruses). It is unclear whether SARS-CoV-2 directly affects neurons or other CNS cells, and if so, whether the virus will be destroyed in these cells and brain regions after "recovery" from COVID-19 [64]. In pathological examination of the tissues of patients who "recovered" from the infection, but died for other reasons, an active virus in the lung tissue was revealed [64]. Findings suggest that the virus does not disappear from the body after "recovery" in some patients, but remains in the mucous membrane of the

upper respiratory tract, which increases the likelihood that SARS-CoV-2 can escape from immune surveillance and exist in the body for a long time [64]. If the replicative virus persists in the CNS after clinical recovery, it can have serious consequences for the brain. Even the presence of an abortive infection or an inflammatory response to the virus can adversely affect cell function. The above results of several literature reviews indicate not only the insufficiency or inconsistency of statistical data as for neurological complications after infection, but also the need for further study of all early and late manifestations of neurological disorders and diseases in COVID-19, clarification of the mechanisms of their development and treatment methods taking into account pathogenesis and clinical forms of infection.

Thus, it is necessary to study many issues related to neurological complications after COVID-19, notably the neuroinvasive and neurotropic properties of the virus, the mechanisms of direct or indirect action of the virus on the nervous system, the role of neuroinflammation and immunopathological responses, the nature of neurological disorders in mild and asymptomatic manifestations of infection, acute and Long COVID-19 and after vaccination.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This article is a literature review, therefore no ethics committee approval was required.

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