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Neurological aspects of COVID-19

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Abstract

The coronavirus disease COVID-19 began to spread worldwide in December 2019 from the city of Wuhan (China). COVID-19 is often accompanied by fever, hypoxemic respiratory failure and systemic complications (for example, gastrointestinal, renal, cardiac, neurological, and hepatic lesions), thrombotic phenomena. Central nervous system damage is caused by the primary effect on it, direct neuroinvasion of the virus, and more often by secondary effect due to systemic hyperinflammation. Neurological manifestations include fatigue, headache, insomnia, and olfactory/taste disorders. Neurological manifestations and complications of COVID-19 are diverse: (1) cerebral circulatory disorders, including ischemic stroke and macro/microhemorrhages; (2) encephalopathy; (3) para/postinfectious autoimmune complications, such as Guillain–Barre syndrome; (4) meningoencephalitis; (5) neuropsychiatric complications (psychosis and mood disorders). In terms of pathogenesis, neurological disorders in COVID-19 can be caused by neurotropicity and neurovirulence of SARS-CoV-2, cytokine storm, hypoxemia, homeostasis disorders, as well as their combined effects. COVID-19 adversely affects the course and prognosis of chronic neurological disorders in comorbid patients. The review highlights the need for vigilance to early neurological complications in patients infected with SARS-CoV-2 and other coronaviruses, especially since some neurological complications may precede respiratory manifestations.

Keywords: SARS-CoV-2, coronavirus infection, neurological manifestations, neurological disorders, neurotropicity, neuroinvasion.

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The coronavirus disease-2019 (COVID-19) pandemic has already gone down in history as an international emergency incident. In December 2019, in the city of Wuhan, China, the capital of Hubei province, an outbreak of a new coronavirus infection occurred with clinical manifestations such as fever, dry cough, dyspnea, and pneumonia [1, 2]. On January 30, 2020, the outbreak was identified as a public health emergency of international concern [3, 4]. On February 11, 2020, the World Health Organization (WHO) assigned the new coronavirus infection the official name, COronaVIrus Disease-2019. On March 11, 2020, the WHO officially declared COVID-19 a global pandemic, which became the eleventh in the XX–XXI centuries [5–9].

Five scientific research databases (PubMed, Scopus, Web of Science, Medline, eLibrary) were analyzed to describe and systematize the range of neurological complications in patients with COVID-19, where we found 15,887 publications from December 2019 to May 2021. The publications draw attention to the spectrum of early and long-term complications in COVID-19 with an emphasis on neurological manifestations.

Since the beginning of the XXI century, new strains of coronaviruses appear from time to time in different countries worldwide. In 2002, a severe acute respiratory syndrome (SARS) caused by the SARS-coronavirus (CoV) was identified. In 2012, the Middle East Respiratory Syndrome-CoV was first identified, which led to the onset of the respiratory syndrome [10].

SARS-CoV-2 penetrates the cell membrane at the site of the location of the transmembrane receptors for the type 2 angiotensin-converting enzyme (ACE2) and gain access to the host cell [11–13]. However, different strains of coronaviruses use different host receptors through different receptor binding domains. The ACE2 receptor is highly expressed in the cells of the alveolar epithelium, oral mucosa, heart, kidneys, lymphoid organs, testes, intestines, urinary tract, and brain [14].

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SARS-CoV-2 can cleave its S-protein by the host cell transmembrane protease serine 2 (TMPRSS2) [15]. However, the distribution of TMPRSS2 is limited in the cells of the prostate gland, respiratory epithelium, salivary glands, kidneys, liver, and stomach, as well as the small and large intestines [16, 17]. TMPRSS2 is regulated by androgens, which may elucidate the higher susceptibility of males to the severe forms of COVID-19.

Protease TMPRSS4 and cathepsin L also promote the infection of human enterocytes of the small intestine and 293/hACE2 cells [18]. Consequently, the tissue expression patterns of TMPRSS2, TMPRSS4, and cathepsin L become another decisive factor in determining the virus tropism.

The SARS-CoV-2 virus can also use other target proteins to enter the cell. Peptidases, ANPEP, DPP4, and ENPEP, are assumed to be receptors for coronaviruses [19]. Additionally, SARS-CoV-2 can infect immune cells by receptor-dependent fusion of the virus S-protein with the host cell membrane and lead to their apoptosis [20–22].

SARS-CoV-2 more often infects elderly people compared to other viruses of this family [23–25]. Mortality from COVID-19 is high among elderly patients (over 70) and people with chronic diseases. In children under 16 years of age, the severe form of COVID-19 is accompanied by multisystem inflammatory syndrome, which may determine the disease outcome. In some cases, neurological complications are less severe [26, 27]. The indicator of morbidity and mortality is decreasing in groups aged 25–49 years, but increased excess mortality in the age groups of 45–64 years old was observed [28].

Numerous studies revealed that the virus causes irreversible damage to many organs, especially the lungs, causing respiratory failure. However, this respiratory failure caused by damage to the respiratory center in the medulla oblongata or by pulmonary pathology remained controversial. The extent of SARS-CoV-2 damages in the central nervous system (CNS) and the association of neurological symptoms with secondary mechanisms remain unanswered [29]. Whether SARS-CoV-2 is neurotropic and contributes to post-infectious neurological complications remains debatable.

The neurological manifestations in patients with COVID-19, as well as the isolation of other human coronaviruses from neurological samples, support the idea of the possible neurotropicity of the virus [30–32]. To date, the exact mechanisms of the viral penetration into the CNS are not fully understood; however, scientists suggest that the virus can enter the body through the retrograde pathway, i.e., along the cranial nerves (olfactory, trigeminal, and vagus), and then penetrate the CNS tissue using the transsynaptic transfer mechanism [33, 34].

The dissemination of SARS-CoV-2 through the ethmoid plate has been established to result in brain damage. Therefore, the olfactory bulb is the only part of the CNS that is not protected by the dura mater [35]. There is evidence that SARS-CoV-2 reaches the brainstem through the vagus nerve and causes damage to its nucleus, where the centers of respiratory and cardiac control are located, this, in turn, exacerbates the damage caused by a primary infection in the lungs [36].

The endothelial cells of the blood-brain barrier (BBB) are also a possible neuroinvasion pathway [37, 38]. There are two possible mechanisms through the BBB; the first mechanism represents the infection and transfer of the virus into vascular endothelial cells, and the second mechanism is the infection of leukocytes that pass through the BBB, and this phenomenon is called the "Trojan horse" mechanism.

Once in the bloodstream, SARS-CoV-2 can bind to the endothelial ACE2 receptors [39, 40] and destroy the BBB, causing edema, intracranial hypertension, and/or penetration into the CNS. For the first time, the presence of the SARS-CoV-2 gene in the cerebrospinal fluid was identified in a patient with COVID-19 and neurological disorders on March 4, 2020, by researchers from Beijing Ditan Hospital (China) [41].

Therefore, in the brain, ACE2 receptors are widely expressed in many of its regions, namely the dorsal complex of the vagus nerve (solitary nucleus, Postema region, and cardioinhibitory center) and the brainstem, especially in the solitary nucleus, as well as in the basal ganglia, in the solitary tract nucleus, the paraventricular nucleus in gray matter, substantia nigra, posterior cingulate cortex, and olfactory bulb [42]. Thus, the brain can be assumed as more vulnerable to COVID-19 infection.

Respiratory distress that occurs during a SARS-CoV-2 infection can be caused by a dysfunction in the brainstem cardiorespiratory center. Many patients with COVID-19 have nonspecific neurological symptoms, such as dizziness, nausea, vomiting, and headache, even if laboratory tests do not reveal clinical symptoms of nervous system damage [43]. These nonspecific neurological symptoms may indicate the neurotoxic effect of hypoxemia and cytokine storm noted in patients with severe COVID-19.

The first published retrospective cohort study by Ling Mao et al. from Wuhan revealed that in a sample of 214 patients with a confirmed COVID-19 diagnosis, 36% of the patients had neurological complications. They made an important

discovery, demonstrating that 78%–88% of the patients with severe COVID-19 have signs of more serious CNS damage in the form of impaired consciousness and cerebrovascular disorders, hypogeusia, and hyposmia than patients with the mild disease [44].

Another more recent report by L. Mao revealed that a third of patients with COVID-19 had nonspecific neurological manifestations, including dizziness (16.8%), headache (13.1%), loss of consciousness (7.5%), and seizures (0.5%) [44].

Two systematic reviews and meta-analyzes by Chinese scientists revealed that headache and dizziness are among the most common neurological symptoms in patients with COVID-19, as well as other cranial symptoms and anosmia/ageusia. Thus, headaches can occur both during the disease and after recovery. Headache is possible even in the absence of fever, which includes migraine, tension, and cluster headache.

A study is of interest revealed that the frequency of headaches at the disease onset was higher in patients with COVID-19 having gastrointestinal symptoms than in patients without gastrointestinal disorders. According to the authors, the feature revealed is due to a higher level of fever and more pronounced electrolyte disorders in patients with gastrointestinal manifestations [45].

A study conducted in Spain [46] identified different types of headaches in 112 patients with COVID-19. The study groups were divided into several cohorts based on the type of headaches. Most of the patients had mild/moderate headaches, while a quarter of patients, especially females and young people, had severe "migraine-like" headaches without evidence of migraine or tension headaches, or other neurological disorders in history. Many patients noted pain resistance to common analgesics or a high rate of headache recurrence during active COVID-19. Patients who had migraine before the COVID-19 described another nature of headache, different from migraine, with an infectious lesion, but, just like migraine, noted the pronounced symptoms of phono and photophobia [47].

The first factor leading to headaches in COVID-19 may be the direct penetration of the virus into the trigeminal nerve endings in the nasal cavity and their direct damage. In their study, P.J. Goadsby et al. proved that angiotensin II increases the level of circulating calcitonin gene-related peptide in the blood, which is a key neuropeptide in migraine that provokes the onset of headache, and its antagonists are effective in the treatment of migraine [48].

The next mechanism is the vascular factor, which plays a significant role in increased thrombogenesis, especially in severe disease and multiple organ failure [49, 50]. Microthrombosis can also damage and irritate sensitive nerve endings and cause pain syndrome.

SARS-CoV-2 exposure results in the release of pro-inflammatory mediators (such as interleukin-1β, nuclear factor κb, prostaglandin E2, and nitric oxide) and cytokines, which increase the sensitivity of nociceptive receptors to pain mediators (histamine and bradykinin) [51].

The severity of inflammation and hypoxia, which correlates with the disease severity, is also significant in headaches intensity [52]. Persistent headache is often a prodromal, difficult to treat a symptom of COVID-19 for which patients may seek medical help [53].

COVID-19, like a headache trigger, can cause chronic pain disorders, such as persistent daily headaches. However, for a complete assessment of headache persistence, these patients must be followed up for at least 3 months. A significant number of patients without a headache history, headache persists for >6 weeks, even after the elimination of other COVID-19 symptoms [54].

Sudden anosmia is one of the first and significant symptoms of COVID-19 but is not accompanied by swelling of the nasal mucosa or rhinitis. Moreover, sudden anosmia can occur with a sense of well-being and an unimpaired disease course [55]. Along with these forms, olfactory disorders can manifest themselves in the form of illusions, distorted perception, and olfactory hallucinations (parosmia and phantosmia in 32.4% and 12.6% of the cases) [56, 57]. The American Academy of Otolaryngology and the British Association of Otorhinolaryngology recommend adding these symptoms to the list of primary screening for COVID-19 [58].

The United States of America scientists revealed that the frequency of ageusia and anosmia was higher in the COVID-19-positive group compared with the negative group (anosmia/olfactory disorder in 68% vs. 16% and ageusia in 71% vs. 17% of cases). Concurrently, the majority of patients in this study were outpatients and did not require hospitalization [59]. The authors suggested that SARS-CoV-2 probably spread transnasally in outpatients, contrary to critically ill patients in whom the virus spread was most possibly pulmonary.

Scientists suppose that SARS-CoV-2 cannot directly enter the olfactory sensory neurons, but can instead target sustentacular cells, mucosal cells, Bowman's cells, and olfactory stem cells. Additionally, SARS-CoV-2 can cause a cytokine storm in the olfactory system and enhanced immunological response. The release of cytokines can contribute to olfactory sensory neuron damages [60, 61].

SARS-CoV-2 reaches the brain if the virus first enters the cells of the olfactory epithelium with a high level of ACE2 expression, and then proceeds to mature neuronal cells with a low level of ACE2 expression, and then transported from them along the olfactory axons to the brain.

Several hypotheses have been proposed to explain anosmia. Some authors believe that anosmia is in some way associated with olfactory nerve inflammation, and not with damage to the structure of receptors; however, other authors consider it as the result of nerve damage or olfactory nerve inflammation, which requires further research [62].

In the neurological status of some patients, the symptom of ageusia/hypogeusia was noteworthy. Based on the survey, several clinical forms were distinguished, namely ageusia (1.4%–5.6%), hypogeusia (47.5%), and dysgeusia (21.1%). Branches of the facial nerve, except *n. lingvalis*, provide the perception of salty, sour, bitter, and sweet tastes in the front two-thirds of the tongue, remain intact. The targets of coronaviruses are (a) chemoreceptors of the lingual papillae, epithelial cells of the mucous membranes of the oral cavity and pharynx; (b) afferent nerve fibers of the cranial nerves; (c) temporal lobe cortex and brain stem with viremia and retrograde propagation [63]. The smell and taste perversions arising at the stage of initiation of apoptosis are reversible in most patients [64].

Acute cerebrovascular accident is possible in the later disease stages and more often in patients with severe respiratory failure. In patients who had a stroke, the risk of death from COVID-19 increases threefold [65]. Some patients with COVID-19 were admitted to the hospital with hemiplegia, without respiratory symptom history. Avula et al. revealed that four patients with a positive polymerase chain reaction (PCR) result had onset of stroke symptoms [66].

Moreover, F. Al Saiegh et al. and B. Neumann et al. presented two cases with confirmed infection caused by SARS-CoV-2, with concomitant neurological symptoms of stroke, but at the same time negative cerebrospinal fluid analysis. In one case, a 31-year-old male patient without a history of comorbidities was admitted with subarachnoid hemorrhage, and later a positive nasopharyngeal PCR result for COVID-19 was obtained. In another case, a 62-year-old female patient was admitted with a hemorrhagic stroke without any COVID-19 symptoms and a positive nasopharyngeal PCR test result [67, 68].

Hemiplegia as a result of stroke, which arose in the presence of COVID-19, occurred in elderly patients with cardiovascular diseases to a greater extent than in middle-aged patients. This indicates that COVID-19 and stroke have similar risk factors.

Goldberg et al. and Larson et al. in New York [69, 70] revealed cases of ischemic stroke in patients aged 33 and 37 years old with a mild course of COVID-19, without a history of acute cerebrovascular pathology. These cases highlight the possibility of comorbidity between COVID-19 and stroke.

The basis of the pathogenesis of the effect of the SARS-CoV-2 virus on the body cells is a cytokine storm, in which the level of pro-inflammatory cytokines, including interleukins-1 and -6, increases significantly. Rostami and Mansouritorghabeh provided evidence that patients with COVID-19 can develop severe coagulopathy defined as "COVID-19-associated coagulopathy" [71].

A relationship has been established between multifocal brain lesions with coagulopathy and antiphospholipid antibodies to cardiolipin, β2-glycoprotein I, and immunoglobulins A and G [72]. Y. Zhang et al. from China revealed that patent with COVID-19 developed multiple bilateral ischemic cerebral infarctions. The antiphospholipid antibodies and hematological parameters registered in them indicated acquired thrombophilia [73].

Some critically ill patients with COVID-19 have a significant tendency for clot generation. In such cases, anticoagulant intake appears to be associated with a better prognosis in patients with severe COVID-19 due to a reduced risk of venous thromboembolism [74]. A decreased activated partial thromboplastin time of blood, increased prothrombin index, significantly increased levels of D-dimer and fibrin, as the most significant marker of local and systemic thrombosis, indicate the presence of hypercoagulability.

In hemorrhagic stroke, impaired hemostasis, BBB permeability in inflammatory vasculopathy, and uncontrolled arterial hypertension are of paramount importance. Scientists from Iran suggest that angiotensin II receptor dysfunction due to SARS-CoV-2 invasion can lead to water and sodium dysregulation, which will lead to arterial wall rupture [75]. ACE2 receptors regulate the blood pressure, and, according to studies, the SARS-CoV-2 spike protein can interact with ACE2 receptors, which leads to increased blood pressure and an increased risk of cerebral hemorrhage [76].

S. Elgamasy et al. described several cases of recurrent transient generalized tonic-clonic seizures in patients with COVID-19 who did not have a history or family history of epileptic seizures. The incidence of this complication in COVID-19 does not exceed 10% [77].

Several hypotheses have been proposed to explain epilepsy that is associated with COVID-19. First, the release of inflammatory cytokines, tumor necrosis factor α, can trigger neuronal hyperexci-

tability through the activation of glutamate receptors, leading to episodic seizures [78]. Secondly, the structural and functional disorganization due to neuroinflammation, encephalitis, hypoxemia, and hypocalcemia [79]. Third, the renin-angiotensin system dysregulation in the brain induces seizures and epilepsy when hyperactivation of angiotensin II/angiotensin I receptor signaling in astrocytes and microglia occurs [80].

The literature revealed that the relationship between myalgia and SARS-CoV-2 remains unknown and is subject to discussion [81]. Several types of myalgia are registered in patients infected with SARS-CoV-2, namely critical myopathy, acute quadriplegic myopathy, thick filament myopathy, and necrotizing myopathy. Critical myopathy is typically non-necrotizing diffuse myopathy with associated fatty degeneration of muscle fibers, fiber atrophy, and fibrosis, and maybe a precursor of acute necrotizing myopathy. It is characterized by extensive myonecrosis with vacuolization and phagocytosis of muscle fibers and is associated with multiple organ dysfunction.

An American study by G. Lippi et al. revealed two cases of rhabdomyolysis with creatine phosphokinase levels of >11,000 U/L in patients with COVID-19, which may indirectly indicate necrotizing autoimmune myositis caused by SARS-CoV-2. Of whom, one case was an 88-year-old male from New York with acute painful bilateral weakness of the proximal lower extremities and hypercreatinekinasemia (13,581 U/L). Additionally, there was a 60-year-old male patient from Wuhan with 6-day COVID-positive pneumonia and fever, who developed painful proximal muscle weakness with hypercreatinekinasemia (11,842 U/L) and increased level of C-reactive protein after 7 days, despite an improvement in his clinical condition.

G. Lippi et al. concluded that increased levels of lactate dehydrogenase and creatine kinase are possible in patients with severe COVID-19. Severe rhabdomyolysis can be a rare late COVID-19-associated complication, as well as serious liver and kidney damage [82]. The patients with severe course develop weakness due to muscle fiber atrophy and/or critical painful myopathy (and/or polyneuropathy).

H. El Otmani et al. suggest that myalgia does not necessarily have to accompany severe course COVID-19, therefore its presence cannot serve as a reliable prognostic factor for severe COVID-19 [83].

Guillian-Barré syndrome (GBS) may be preceded by viral illness (<3 weeks) in 70% of cases [84]. Evidence was reported that the S-protein of the SARS-CoV-2 virus can bind to glycoprotein and sialic acid-containing gangliosides on the cell surface, thereby increasing its viral transmission. In GBS, cross-reactivity can occur between epitopes inside the gangliosides carrying the S-protein of SARS-CoV-2 and glycolipids of superficial peripheral nerves. Antibodies produced by the immune system to combat the virus cross-react and bind to peripheral nervous system components, causing areflexia [85].

GBS is believed to be a symptom of the new coronavirus, but many questions remained controversial. The clinical presentation of COVID-19 includes many neurological manifestations of varying severity. The "post-infectious" manifestation described in the literature between infection with the main causative agent of the disease and the development of neurological complications is the classic GBS phenotype [86].

An infectious agent in multiple sclerosis plays a triggering role in genetically predisposed patients [87]. Infiltration with autoreactive $CD4^+$-T lymphocytes of the CNS after activation in the periphery becomes a critical condition in multiple sclerosis pathogenesis. The evaluation of pro-inflammatory cytokines (interleukins-1β, -6, and -8), Th1 cytokines (interferon γ, tumor necrosis factor α, interleukins-2 and -12), and Th2 cytokines (interleukins-4, -5, and -10) in the blood serum of patients with SARS within 2 days after admission to the hospital revealed a significant increase in the level of interleukins-12, -6, -8, -10, and interferon γ [88].

Additionally, Sonar et al. demonstrated that interferon γ promotes transendothelial migration of $CD4^+$-T cells from the apical to the basal side of the endothelial monolayer. These data demonstrate that interferon γ, produced in response to infection and inflammation, can contribute to BBB destruction and $CD4^+$-T cell migration to the brain.

The release of myelin components can also trigger an autoimmune attack. Infection or activation of astrocytes and microglia can release inflammatory mediators that can damage oligodendrocytes, thereby exacerbating the pathology. These data are important since the BBB breakdown in COVID-19 precedes the development of new foci of multiple sclerosis [89].

Thus, endothelial cell damage caused by infection with SARS-CoV-2 results in disruption of the BBB integrity, thereby contributing to the progression of multiple sclerosis.

Daily, the number of publications about the relationship between COVID-19 and significant neurological complications, both in the acute period and after it, is growing. However, due to the short duration of patient follow-up, the association of this infection with longer-term neurological sequelae remains controversial. Screening the patients

who recovered is imperative to monitor for any long-term neurological consequences. Nowadays, more data are required to establish the prevalence of short- and long-term consequences of neurological disorders.

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