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Neurological manifestations and complications of COVID-19. A literature review

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ABSTRACT

Introduction. The first case of SARS-CoV-2 infection was identified in December 2019 in Wuhan, China. The disease spread rapidly worldwide and the WHO declared a pandemic on March 11, 2020. Although coronavirus disease 2019 (COVID-19) has been associated primarily with respiratory disorders, more and more research is focusing on neurological manifestations and complications.

Objective. The aim of the review is to systematize and update the knowledge and available research on neurological complications among COVID-19 patients.

Review methods. A systematic search of PubMed and Google Scholar databases was conducted for studies. The following keywords combinations were used: COVID-19, SARS-CoV-2 infection, neurological complications, neurological manifestations, neuroinvasion, neurovirulence.

Results. The disease in most patients is characterized by mild to medium fever, fatigue, dry cough, dyspnea, muscle pain and headache. ACE2, which is the receptor for SARS-COV-2, is ubiquitously expressed in a variety of human organs, including the brain. Following previous reports, these receptors are expressed in both glial cells and neurons. Many studies have reported neurological symptoms and complications among COVID-19 patients. The reported manifestations include: smell and taste disturbance, non-specific symptoms such as myalgia, headache and dizziness, acute cerebrovascular complications, encephalopathy, meningoencephalitis/encephalitis, seizure and complications of the peripheral nervous system.

Conclusion. Healthcare professionals dealing with COVID-19, neuroscientists, and the general public should be aware of the neurological complications of COVID-19. Further studies are needed to assess the incidence of COVID-19 neurological complications in different populations and more analyzes are also required to understand the detailed mechanism of how the virus affects the nervous system.

Key words: COVID-19, SARS-CoV-2 infection, neurological complications, neurological manifestations, neuroinvasion, neurovirulence.

Introduction

Coronaviruses are enveloped positive-stranded RNA viruses that predominantly cause enteric and respiratory infections [1]. They are classified into 4 different genera: alpha, beta, delta and gamma [2]. SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a novel betacoronavirus that causes the disease termed as COVID-19 (coronavirus disease 2019) [3]. The first case of COVID-19 was identified in December 2019 in Wuhan, China. The World Health Organization declared a pandemic on 11 March 2020 [4].

The most common symptoms among patients with COVID-19 include fever, fatigue, dry cough, dyspnea, muscle pain and headache [5], [6]. About 80% of COVID-19 infections occur as a mild respiratory illness, 15% typically need hospital care (usually for moderate to severe pneumonia), and another 5% have critical illness requiring intensive care [7], [8]. WHO indicate that the crude mortality ratio is between 3-5% whereas for seasonal influenza mortality is usually well below 0.1% [8]. Moreover, old age and medical comorbidities such as hypertension, diabetes and obesity are associated with an increased risk of multiple organ failure, mortality and morbidity [9].

Despite the fact that COVID-19 is mainly associated with respiratory disease, neurological manifestations and complications are increasingly recognized. There is

developing evidence that severe acute respiratory syndrome coronavirus 2 can attack nervous tissue, resulting in various neurological manifestations and complications [10], [11]. Interestingly, other betacoronavirus infections, including SARS-CoV and MERS-CoV (which caused outbreaks in 2002 and 2012 respectively) were also associated with neurological manifestations [12], [13].

Objective

The aim of the review is to systematize and update the knowledge and available research on neurological complications among COVID-19 patients. Characterizing the impact of SARS-CoV-2 on the nervous system can be very important in the properly diagnosing infected people as well as in the comprehensive treatment of patients.

Matherials and method

A systematic search of PubMed and Google Scholar databases was conducted for studies. The following keywords combinations were used: COVID-19, SARS-CoV-2 infection, neurological complications, neurological manifestations, neuroinvasion, neurovirulence. In addition, the bibliographies of included studies were scanned to identify other potentially eligible studies. Case reports, case series, retrospective studies, cohort studies and cross-sectional studies were included for further analysis and review. The criteria for eligibility included studies published in English language (or translated to English), those involving patients with COVID-19 and reporting neurological findings. Exclusion criteria included: published in a language other than English, clinical observations with no related neurological symptoms and a lack of related data, pediatric population and studies that only reported nonspecific neurological symptoms.

Description of the state of knowledge

Mechanisms of nervous system involvement by SARS-CoV-2

The mechanisms of the occurrence of neurological dysfunctions in patients with COVID-19 are probably associated directly with infecting various neural cells by SARS-CoV-2 and also can be associated indirectly witch consequences caused by SARS-CoV-2 systematically plus para/post-infectious inflammation in the nervous system [14]. The clinical evidence that SARS-CoV-2 could invade the nervous system is provided by cases of detection SARS-CoV-2 by reverse-transcription polymerase chain reaction (RT-PCR) assay in the cerebrospinal fluid (CSF) of numerous patients with various neurological symptoms. Such cases were reported by e.g. José Cebrián et al. (the case of a 74-year-old woman with positive SARS-CoV-2 CSF by qRT-PCR, presenting headache and impaired consciousness as the main neurologic symptoms) [15] and Johan Virhammar et al. (the case of 55-year-old woman with COVID-19–related acute necrotizing encephalopathy where SARS-CoV-2 RNA was found in CSF 19 days after symptoms) [16]. Furthermore, Andriuta et al. reported the presence of the

anti-SARS-CoV-2 antibodies in the CSF samples of two patients with COVID-19 encephalopathy [17]. Additionally, a case series study concerning neuropathological findings from autopsies of 18 patients with COVID-19 showed atherosclerosis in 14 brains and acute hypoxic injury in the cerebrum and cerebellum with loss of neurons among all patients. The virus was detected by RT-PCR in five brains [18].

Studies indicate that SARS-CoV-2 gains entry into the host cell via ACE2 receptors after priming by transmembrane serine protease 2 (TMPRSS2) targeting the viral spike (S) protein [19]. ACE2 is detected in all tissues, including the lungs, arteries, heart, kidneys, intestines and brain [20]. It is known that ACE2 is an important part of the renin–angiotensin system (RAS) responsible for catalyzing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin (1–7) (a vasodilator) and thus providing a sympatholytic and antihypertensive effect that is protective in neuronal damage [8]. Following previous reports, angiotensin-converting enzyme 2 (ACE2) receptors are expressed in glial cells and neurons, which makes them a potential target of COVID-19. Studies show that the ACE2 binding affinity of the SARS-CoV-2 is 10–20-fold higher than that of the SARS-CoV-1 what indicate a higher risk of neurologic infection in COVID-19 patients [21]. Despite the fact that in the CNS, ACE2 receptors are expressed in the spinal cord, cortex, hippocampus, cerebellum and other brain regions, serine protease TMPRSS2, which is also required for SARS-CoV-2 entry to cells, is only weakly expressed in brain. These findings may suggest that direct virus infection is not the main mechanism of CNS damage. The majority of CNS complications might result from indirect effects of COVID-19, such as hypoxia and anaerobic metabolism in the brain because of alveolar gas exchange disorders caused by viral proliferation in the lung tissue cells, coagulation dysfunction and neuroinflammation [8], [22].

SARS-CoV-2 may enter the nervous system mainly by two routes: transneuronal or hematogenous route [10]. One of the most probable routes of neuroinvasion of SARS-CoV-2 is via the olfactory system. Invasion by this route involves viruses infecting cells of the olfactory epithelium that have high ACE2 and TMPRSS2 expression [23]. Once the olfactory epithelial cells become infected, the virus can travel transneuronally through axons of the olfactory receptor neurons or by non-neuronal cells up to the olfactory bulb [24]. Another potential route of SARS-CoV-2 infection into the brain could be through damaged blood-brain barrier (BBB). The BBB is formed by the highly specialized endothelial cells, astrocytes, pericytes, mast cells and in the healthy state prevents the breach by pathogens [25]. Nevertheless, if there is inflammation and immunosuppression, invasion of viruses can occur. The SARS-CoV-2 virus in the blood may directly infect brain endothelial cells and transendothelially disseminate virus into brain parenchyma by the damaged BBB, which could be compounded by viral infection and cytokin storm [14]. SARS-CoV-2 may also enter the CNS via circumventricular organs and/or choroid plexus, where the BBB is absent [26]. Furthermore, the “Trojan horse” mechanism of neuroinvasion should also be considered. In this strategy of neuroinvasion, the virus hides inside innate immune cells, which traffic across the permeabilized BBB utilizing specific chemokine receptors and can further infect neurons and glial cells. It has been shown that ACE2 receptor is expressed on haematopoietic cells, including monocytes and lymphocytes. Thereupon it is possible that SARS-CoV-2 could infect monocytes and lymphocytes and traffic across the BBB and further infect neural cells

[25]. All these pathways may lead to neurological and/or neuropsychiatric complications by direct infections of the CNS or PNS.

Neurological manifestations and complications

The retrospective study by Mao et al. was one of the first study to assess the nerological complications in COVID-19 and included 214 patients. It was reported that 36.4% patients had central nervous system symptoms (CNS), 8.9% peripheral nervous symptoms (PNS) and 10.7% skeletal muscle symptoms [27]. Since that study, more neurological complications have been reported from all over the world. Neurological complications occur more commonly than initially thought and estimates range from 36% to 84% [8].

The most common neurological manifestations reported in COVID-19 are smell and taste disturbance. In the European retrospective study carried out by Lechien and colleagues olfactory and taste dysfunctions were reported in 85.6% and 88.0% of 417 patients, respectively. There was a significant association between both dysfunctions. The most common type of smell disorder was anosmia. Other smell disorders reported were hyposmia, phantosmia and parosmia. Additionally, females were more often affected by olfactory and gustatory dysfunctions than males [28]. Similarly, in the cross-sectional study conducted by Speth et al. the prevalence of olfactory disorders was about 61.2% and symptoms severity was correlated with the severity of taste disorders. Moreover, smell and taste disorders strongly correlated with younger age and female sex [29]. According to a systematic review by Chen et al. olfactory and gustatory disturbance are more frequently reported in COVID-19 patients with mild or moderate disease as compared to severe or critical disease courses [22]. Kaye and colleagues reported that anosmia can be the initial manifestation of COVID-19 and may be crucial in timely identification of people infected with SARS-CoV-2 who may be unconsciously transmitting the virus [30].

The most common non-specific neurological symptoms among patients with COVID-19 are myalgia, headache and dizziness. According to the meta-analysis by Favas et al. the overall estimated prevelence of myalgia was 19.3%, headache – 14.7% and dizziness – 6.1% [31]. Clinical and epidemiological characteristics of patients with mild-to-moderate COVID-19 was described by Lechien et al. in a group of 1420 patients with positive diagnosis of COVID-19. The most common symptoms were headache, loss of smell, nasal obstruction, cough, asthenia, myalgia, rhinorrhea, gustatory dysfunction and sore throat with headaches occurring in 70.3% and myalgia in 62.5% of patients [32]. Another study considering non-specific neurological symptoms was carried out by Karadaş and colleagues in a cohort of 239 patients. 83 patients displayed neurological symptoms: headache was reported by 64 patients and dizziness by 16 patients [33]. Moreover, an increase in creatine kinase (CK), lactate dehydrogenase (LDH) and myoglobin were also reported among COVID-19 patients with myalgia, what can be caused directly by viral invasion in skeletal muscles, which are also known to express the ACE2 receptors, or indirectly by a systemic inflammatory response manifested by a cytokine storm, subsequently causing muscle injury [6].

Several studies reported patients developing acute cerebrovascular complications secondary to SARS-CoV-2 infection. Mao et al. detected that 2.8% (6 out of 214 hospitalized patients: 5 patients with ischemic stroke and 1 with cerebral hemorrhage who died later of respiratory failure) developed acute cerebrovascular events, of which the vast majority had

severe critical disease course [27]. Another study by Helms and colleagues found cerebrovascular events among 3 patients out of 58. 2 asymptomatic patients had a small acute ischemic stroke with focal hyperintensity and 1 patient had a subacute ischemic stroke [34]. In a single center, retrospective, observational study Li et al. reported 11 cases of cerebrovascular disease out of 219 patients with confirmed SARS-CoV-2. Of these patients, 10 were diagnosed with ischaemic stroke and 1 had intracerebral haemorrhage. Patients, who developed acute cerebrovascular events were significantly older, more likely to present with severe COVID-19 and also more likely to present with cardiovascular risk factors, including hypertension, diabetes and previous medical history of cardio-cerebrovascular diseases. In addition, laboratory parameters in patients with CNS symptoms were shown to be different from other COVID-19 patients, with higher white blood cells and neutrophils, decreased lymphocytes and platelets counts, eleveted CRP and D-dimer levels [35].

A potentially fatal presentation of SARS-CoV-2 is the development of encephalopathy or/and meningoencephalitis. Symptoms can range from the typical headache, fever, and nuchal rigidity to more severe symptoms of brain involvement such as sensory disturbances, agitation, focal neurological deficits, seizures or even coma. Encephalopathy in COVID-19 may be a direct viral effect due to neuroinvasion, an immune-mediated pathology triggered by the virus, indirect immunopathology due to blood–brain barrier dysfunction or a combination of all three [8]. Furthermore, patients with prolonged attendance in the intensive care unit had a higher rate of encephalopathic complications than usually expected. Previous studies indicated that this problem may be caused by a long-term administration of high doses of sedatives and anesthetics during treatment of severe respiratory disease [36]. Several case reports of COVID-19-related meningoencephalitis, encephalitis and encephalopathy have been published. One of the first cases of viral encephalitis was recorded in Japan. A 24-year-old man presented with unconsciousness and generalized seizures 9 days after the first consultation with a doctor because of non-specific symptoms of fever and fatigue. Brain imaging showed signs of right lateral ventriculitis and encephalitis, mostly focused on the right mesial temporal lobe and the hippocampal region. Interestingly, SARS-CoV-2 RNA was detected in his CSF, but nasopharyngeal swabs remained negative [37]. Numerous cases of encephalitis/encephalopathy associated with SARS-CoV-2 infection were reported since then. For instance, Zoghi et al. described the case of a previously healthy 21-year-old male who developed encephalomyelitis with atypical demyelination pattern revealed by MRI [38]. Duong and et al. reported the case of an obese 41-year-old woman diagnosed with meningoencephalitis as neurologic complication of COVID-19, showing worsening encephalopathy with disorientation and hallucinations. Symptoms evolved in lethargic status and then agitation [39]. Cases of encephalopathy were reported also in a retrospective study carried out by Scullen and colleagues. They categorized neurologic complications associated to COVID-19 based on brain imaging or electroencephalography (EEG) of 76 patients. 27 of them had positive neurological examination which revealed encephalopathy in 20 cases and acute necrotizing encephalopathy in 2 patients [40]. What is more, Farhadian et al. in their case report of a 78-year old woman with SARS-CoV-2 infection and associated neuroinflammation showed elevated levels of cytokines like IL-6, IL-8, TNF- α, β2-microglobulin, IP-10, MCP-1 in CSF. These inflammatory cytokines produced by immune

cells within and outside of the CNS can conduce to neurological complications among COVID-19 patients [41].

Seizures as a rather sinister complication of COVID-19 were also reported in some cases. It has been hypothesized that complications of this type may occur due to a decreased seizure threshold caused by a cytokine storm [42]. Electrolyte and metabolic disturbances or hypoxia may also contribute to the occurrence of seizures. In addition, fever itself may lower the seizure threshold and therefore may trigger seizures in a patient with epileptic syndromes [10]. According to the meta-analysis by Favas et al. cases of all types of seizures like febrile seizures, focal seizures, generalized tonic-clonic seizures, myoclonic status epilepticus, status epilepticus and non-convulsive status epilepticus were reported in COVID-19 patients [31].

There is a less substantial but still relevant number of studies reporting effects of SARS-CoV-2 on peripheral nervous system. For instance, Homma et al. described the case of a 35-year-old Japanese woman who showed facial nerve palsy secondary to COVID-19 [43], Abdelnour et al. described the case of a 69-year-old man with a medical history of hypertension, type 2 diabetes mellitus and mild chronic obstructive pulmonary disease, who showed numbness on both legs and decreased muscle strength as secondary symptoms of SARS-CoV-2 infection [44] and the aforementioned Karadaşa and colleagues have also reported complications of the peripheral nervous system in patients with COVID-19, with the most commonly reported conditions such as trigeminal neuralgia, glossopharyngeal neuralgia, vaso-glossopharyngeal neuralgia, myalgia, restless leg syndrome and Guillain-Barré syndrome (GBS) [33]. There are multiple reports of GBS in patients with confirmed COVID-19. Guillain-Barré syndrome is associated with the phenomenon of molecular mimicry between viral proteins and peripheral nerve proteins (e.g. gangliosides), leading to an autoimmune disorder in which the body's immune system mistakenly attacks peripheral nerves and damages their myelin insulation [10].Toscano et al. reported a series of 5 patients of COVID-19 with GBS, with the interval between the onset of fever, cough and symptoms of GBS ranging from 5 to 10 days [45]. In October 2020, the results of the meta-analysis by Imran Hasan et al., which included 61 patients with Guillain-Barré syndrome and laboratory-confirmed SARS-CoV-2 infection, were published. Two-thirds (68.9%) of patients were male and the median age of patients was 57 years and fifty-seven (96.6%) patients previously had COVID-19 related symptoms, including fever, cough, anosmia and ageusia. The time interval between the first symptoms of SARS-CoV-2 infection and the onset of GBS symptoms was 14 days on average. [46]. Cases of Miller Fisher syndrome (MFS) were also reported. Reyes-Bueno et al. described a case of 51-years-old female diagnosed with MFS two weeks after COVID-19 with weakness in the lower limbs and double binocular vision. RTPCR to SARS-CoV-2 was negative but immunoglobulin G was positive [47]. Manganotti et al. also reported a case of a 50-year-old woman that developed SARS-CoV-2 pneumonia and was admitted at the COVID-19 dedicated unit where she developed neurological symptoms 10 days after admission with a diagnosis of Miller Fisher syndrome [48]. Moreover, Gutierréz-Ortiz and colleagues stated a case of MFS associated with a positive serum GD1b-IgG antibody [49].

Conclusions

SARS-CoV-2 infection has turned out to be a global problem and has affected millions of people. The disease, which was initially considered to be a respiratory disorder, has evolved

into a complex multi-organ disease. As research shows, neurological symptoms are common in COVID-19 and based on the large number of cases reported daily from around the world, the incidence of neurological symptoms may continue to increase. Healthcare professionals dealing with COVID-19, neuroscientists, and the general public should be aware of the neurological complications of COVID-19. Moreover, it should be emphasized that patients with a more severe course of the disease show more symptoms from the central nervous system, which may further worsen their clinical condition. Further studies are needed to assess the incidence of COVID-19 neurological complications in different populations and groups with different disease severity. More analyzes and pathophysiological studies are also required to understand the exact and detailed mechanism of how the virus affects the nervous system.

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