Neurological Involvements of SARS-CoV2 Infection

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Received: 11 May 2020 / Accepted: 11 August 2020 / Published online: 16 October 2020
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Abstract
COVID-19 is a pandemic viral infection caused by a novel coronavirus, SARS-CoV2, which is a global concern of the twenty-first century for its rapid spreading in a short period. Apart from its known acute respiratory involvements, the CNS manifestations of COVID-19 are common. These neurological symptoms are diverse and could range from mild nonspecific or specific symptoms such as the loss of various sensory perceptions, the worrying autoimmune Guillain–Barré syndrome, to the life-threatening acute disseminated encephalomyelitis, and the CNS-mediated respiratory distress. An autopsy report documented the presence of SARS-CoV2 in brain tissues of a COVID-19 patient. However, there is no definite conclusion on the mechanisms of SARS-CoV2 neuroinvasion. These proposed mechanisms include the direct viral invasion, the systemic blood circulation, or the distribution of infected immune cells. Concerning these different neuropathophysiologies, COVID-19 patients who are presenting with either the early-onset, multiple, and severe CNS symptoms or rapid respiratory deterioration should be suspected for the direct viral neuroinvasion, and appropriate management options should be considered. This article reviews the neurological manifestations, the proposed neuroinvasive mechanisms, and the potential neurological sequelae of SARS-CoV2.

Keywords COVID-19 · SARS-CoV2 · Neuroinvasion · Severe acute respiratory syndrome · Angiotensin-converting enzyme 2 receptor

Introduction
The pandemics of COVID-19 affect global citizens and drastically alter our living norms. The causative virus for the disease is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a positive-stranded RNA virus that belongs to the Coronavirusidae family [1]. Other known coronaviruses in this family are the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), which cause severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), respectively [2, 3].

Major clinical manifestations of the coronavirus-induced diseases are related to the pathologies of the upper and lower respiratory tract and the hyperactive immune responses that can be fatal independent from the direct impacts of the causative viruses [2]. Despite its variation by locations and changing over time, the case fatality rate, ranging from 0.2% in Germany to 7.7% in Italy, is relatively low [4]. However, the rapid spreading of COVID-19 cumulates the alarming global death toll [4–8]. Apart from the dominant respiratory involvements, there are reports of various clinical manifestations in multiple organs, including the cardiovascular, urological, musculoskeletal, and neurological symptoms [5, 7, 9].

The frequency of neurological manifestations was up to one-quarter in hospitalized COVID-19 patients [10]. Many of them reported nonspecific symptoms such as dizziness, headache, and confusion, while some had the alteration of consciousness, seizure, and other nerve dysfunctions [11]. A recent autopsy identified the SARS-CoV2 in neural and capillary endothelial cells in the frontal lobe of a COVID-19 patient [12].

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SARS-CoV2 and the host cells [25, 26]. The combination of enzyme 2 (ACE2) receptor, the target of interactions between are known for their expressions of the angiotensin-converting neuropathophysiologies [23, 24]. The neurons and glial cells coronaviruses are likely to contribute to their comparable shared structures and the infection pathways of these 20 particularly in the neurons, of SARS and MERS patients [2, 41]. Without the direct invasion or the distribution through the systemic circulation, these infected

Neurological Manifestations of COVID-19

A Chinese retrospective study of 214 patients, who had the laboratory-confirmed of SARS-CoV2 infection, reported the nervous system symptoms in 78 cases (36.4%), 45.5% in severe and 30.2% in nonsevere COVID-19 [10]. Among these patients, 53 cases had CNS symptoms, including dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy. In comparison, 19 cases showed peripheral nervous systems symptoms such as nerve pain and the reduction in taste, smell, and visual perceptions [10]. The group from University College London Queen Square Institute of Neurology recently reported five significant categories of neurological presentations in COVID-19, i.e., (i) encephalopathy with delirium/psychosis and no MRI or CSF abnormalities, (ii) inflammatory CNS syndromes including encephalitis and acute disseminated encephalomyelitis, (iii) ischemic strokes, (iv) peripheral neurological disorders including Guillain–Barré syndrome and brachial plexopathy, and (v) miscellaneous central disorders [13]. Therefore, the neurological manifestations of COVID-19 are diverse and not uncommon [14, 16].

The mental state alterations or the encephalopathy in COVID-19 could be either the systemic consequences of hyperactive immunologic responses or the direct neuroinvasion of SARS-CoV2, as earlier mentioned in a recent autopsy report [15, 18, 19]. Studies of other coronaviruses reported the SARS-CoV and MERS-CoV RNA in the brain tissues, particularly in the neurons, of SARS and MERS patients [2, 20–22]. Despite the limited evidence in SARS-CoV2, the shared structures and the infection pathways of these coronaviruses are likely to contribute to their comparable neuropathophysiologies [23, 24]. The neurons and glial cells are known for their expressions of the angiotensin-converting enzyme 2 (ACE2) receptor, the target of interactions between SARS-CoV2 and the host cells [25, 26]. The combination of direct viral neuroinvasion and the sequela of systemic hyperactive immune responses could contribute to the neurological manifestations of COVID-19 [23].

Apart from the neurological symptoms, the viral neuroinvasion could partly lead to the respiratory distress in COVID-19, as referred to the evidence of respiratory symptoms in SARS patients from the combined viral-induced impacts on the medullary cardiorespiratory center of the brainstem and the mechano- and chemoreceptors in their respiratory tract cells [27–30]. Although the clinical respiratory distress from pulmonary and neurological pathologies is not precisely similar, the proof of SARS-CoV2’s RNA in human nervous tissues supports the possible contribution of SARS-CoV2 neuroinvasion and the respiratory depression [12, 31].

The Proposed Neuroinvasive Mechanisms of SARS-CoV2

Together with other coronaviruses, SARS-CoV2 potentially invades the nervous tissues through several mechanisms. The oronasal inoculation of coronaviruses in pig models reported the infections in the respiratory tracts, small intestine, peripheral nerve, and the retrograde propagation of viruses into the medullary neurons of the brainstem [32, 33]. SARS-CoV rapidly infected the brain of the human ACE2 transgenic mice via the olfactory bulbs and caused rapid neuronal death without evidence of immune responses [34]. MERS-CoV could enter the thalamus and brainstem via the olfactory nerve [3]. Animal models reported the coronavirus infections in the eye structures with the induced inflammation of the conjunctiva, retina, and optic nerves [35]. Some coronaviruses navigate across the nerve synapses after the oronasal inoculation in the animal models [32, 33]. All these pieces of evidence support the possible mechanism of SARS-CoV2 direct neuroinvasion through the olfactory nerve, possibly across the cribiform plate of the ethmoid bone, and the retrograde dissemination into the CNS tissues [23].

With active SARS-CoV2 infection, the systemic circulation could distribute and enable the virus to enter the cerebral blood flow. The interactions between the SARS-CoV2 spike proteins and their endothelial ACE2 receptors could enhance the compromised blood-brain, endothelial, and nasal epithelial barrier [36, 37]. The inflammation also causes sluggish blood flow, which facilitates these interactions and augments the viral neuroinvasion [20, 23, 38]. Systemic circulation could then be an entering passage of SARS-CoV2 into the CNS.

The in vitro studies of human and rat neuronal cell lines demonstrated their susceptibility to coronaviruses infection [39, 40]. The nucleic acids and RNA of SARS-CoV2 were detected in both alveolar pneumocytes and the macrophages of SARS patients [2, 41]. Without the direct invasion or the distribution through the systemic circulation, these infected
leukocytes can infiltrate into brain tissues through the glial-lymphatic or glymphatic system and serve as the reservoir for the viral delivery in CNS [42, 43].

Although there is no concluded mechanism for SARS-CoV2 neuroinvasion, the virus had already made its presence in the brain tissue of a COVID-19 patient [12]. This possibility should be aware of while assessing the neurological manifestations of COVID-19. Figure 1 summarizes the proposed mechanisms of SARS-CoV2 neuroinvasion.

The Neurological Sequelae of COVID-19

The dominant characteristics of COVID-19 are the excessive host immune responses to the SARS-CoV2 invasion, potentially up to the degree of the fatal “cytokine storm” in severe cases [44]. The disproportion of pro-inflammatory chemokines and cytokines to the interferon-mediated anti-inflammatory responses is prominent in the susceptible hosts with compromised metabolic backgrounds [28, 42, 45–47]. Even without the evidence of CNS viral invasion, the immunologic hyperactivation can induce severe brain inflammation, as shown in the CT and MRI reports of hemorrhagic necrotizing encephalopathy of a COVID-19 female [19]. The sterile inflammation of nervous tissues could already produce the clinical symptoms of neuritis, meningitis, and encephalitis, which eventually lead to reactive gliosis, neuronal dysfunction, and neuronal death [12, 22, 48]. Several immunological consequences, such as the disseminated intravascular coagulation or the endothelial rupture in cerebral capillaries with the accompanied bleeding, can be fatal [23].

![Proposed mechanism for SARS-CoV2 neuroinvasion.](image-url)
The early COVID-19 cases reported the loss of perceptions such as smell, taste, and vision, which are partially the symptoms of inflammatory-induced nerve dysfunctions [23, 49, 50]. Five Italian COVID-19 patients developed the autoimmune Guillain–Barré syndrome after 5 to 10 days following the onset of SARS-CoV2 infection [51]. With these hyperactive immunologic sequelae of SARS-CoV2, the range of COVID-19 neurological manifestations is diverse.

Cumulative animal studies established the detrimental impacts of direct coronavirus invasion in the nervous tissues with the resulting inflammation, degeneration, and death of neurons and glial cells [52–55]. The processes of viral replication within host cells could disrupt the neuronal functions with various clinical manifestations, including seizure, convulsion, loss of consciousness, and ataxia [56, 57]. Interestingly, the laboratory testing in a COVID-19 patient with neurological signs was positive for SARC-CoV2 in the cerebrospinal fluid but was negative for the virus in the nasopharyngeal swab [57]. These findings support the likelihood of SARS-CoV2 direct neuroinvasion independent from the primary respiratory inoculation. The direct viral neuroinvasion should be suspected in COVID-19 patients with either early-onset, multiple, severe CNS symptoms, or rapid clinical deterioration despite the appropriate supportive measures.

Specific Considerations for Neuroinvasion in COVID-19

With the probable SARS-CoV2 neuroinvasion, it is worth considering the specific treatment options in addition to the current COVID-19 management protocol. Apart from the antiviral strategy, there were animal studies on the possibility of modulating CNS excitatory pathways, i.e., the glutamate homeostasis [58–60]. A known N-methyl-D-aspartate (NDMA) receptor antagonist, memantine, improved the symptoms, reduced motor disabilities, and the viral replication in coronavirus-infected mice [58]. Other NMDA receptor blockers, including dizocilpine, agmatine sulfate, and ifenprodil, also reduced the neuronal death, the intraocular pressure (IOP), the reactive gliosis, and the neurodegeneration in the ZIKA-infected mice [59]. A glutamine antagonist, 6-diazo-5-oxo-l-norleucine, reduced CNS leukocyte migration, prevented inflammation, paralysis, and death in mice [60]. With the worsening prognosis of SARS-CoV2 neuroinvasion, these options are probably reserved for compassionate considerations.

Conclusion

COVID-19 is a global concern of the twenty-first century by its rapid spreading to every continent in a short period. Apart from the known respiratory involvements, the CNS manifestations of COVID-19 are common. The neurological symptoms are diverse and could range from mild symptoms such as the loss of various sensory perceptions, the worrying autoimmune Guillain–Barré syndrome, to the life-threatening progressive encephalopathy, and the CNS-mediated respiratory distress. An autopsy report documented the presence of SARS-CoV2 in the brain tissues of COVID-19 patients. However, there is no definite conclusion on its probable mechanisms of neuroinvasion. These proposed mechanisms include the direct viral invasion, the systemic blood circulation, or the distribution of infected immune cells. Concerning these different neuropathophysiologies, COVID-19 patients who are presenting with either the early-onset, multiple, and severe CNS symptoms or rapid respiratory deterioration should be suspected for the direct viral neuroinvasion. At the same time, appropriate management options and specific attention are warranted.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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