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Neurological Involvement of Patients with COVID-19: Proposed Neuroinvasive Mechanisms and Management

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Abstract

The novel Coronavirus Disease 2019 (COVID-19) is a highly contagious virus that has caused tremendous chaos in the world. Generally, respiratory symptoms are dominant manifestations in patients with COVID-19. However, the involvement of other organs, such as the nervous system has also been reported, which elucidates the capability of the virus to induce multi-organ failure. In this regard, the presentation of neurological symptoms in infected patients has raised the concern regarding the neuroinvasive potential of COVID-19. As of today, there is emerging evidence that supports the susceptibility of the nervous system to COVID-19. Undoubtedly, the awareness of these findings can result in the timely management and treatment of patients. In the present article, we documented a brief overview of neurological manifestations, possible neuroinvasion mechanisms of COVID-19, and the management of neurological symptoms in infected patients.

Keywords: COVID-19, Neurological Symptoms, Neuroinvasive

1. Background

As a global pandemic, the novel Coronavirus Disease 2019 (COVID-19), with a high rate of transmission and almost 640,016 confirmed deaths as of 26 July 2020, has caused tremendous chaos in the world and significantly attracted global attention. Generally, coronaviruses (CoVs) are known as the members of the subfamily *Coronavirinae* with non-segmented, positive-sense, single-stranded enveloped RNA, which infect both humans and animals (1). Although most human CoVs, including hCoV-229E, hCoV-OC43, hCoV-NL63, and hCoV-HKU1, are associated with a mild respiratory syndrome, the remaining three, including SARS-CoV, MERS-CoV, and SARS-CoV-2have been found to result in severe acute respiratory syndrome with high fatality (2, 3). Interestingly, similar to SARS-CoV, SARS-CoV-2binds by its s-proteins to the Angiotensin-Converting Enzyme 2 (ACE2) on the surface of human cells (4). ACE2 is distributed in arterial and venous endothelial cells of different human organs, including the skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain, with abundant presence in the epithelia of the lung and small intestine (5). Indeed, this widespread distribution of ACE2 in almost all organs has led to the assumption that SARS-CoV-2, when it enters the bloodstream, can spread all over the human body. In support of this, although the most common feature of COVID-19 in patients is respiratory failure, neurological manifestations have been recently reported by several studies (6-9). In this regard, the neurological symptoms in patients such as nausea, headache, and the loss of smell and taste have raised the concern regarding the neuroinvasive potential of COVID-19 (10). Therefore, in the present review, we discussed the neurological manifestations and possible mechanisms by which COVID-19 invades the Central Nervous System (CNS), and finally, the management of neurological symptoms in infected patients.

2. Clinical Manifestations of COVID-19 Infection

Due to a highly homological sequence between SARS-CoV-2and SARS-CoV, it is not surprising to find similar clinical symptoms for COVID-19, as previously reported for SARS-CoV (11). This possibility becomes more likely, as both viruses bind to the same receptor. Most patients diagnosed

with COVID-19 exhibit typical symptoms, including fever, dry cough, and fatigue at the onset of disease. Based on the clinical studies in China, however, the prevalence of diarrhea is limited in patients (almost 3%) (3, 12). Generally, COVID-19 infection has been associated with pneumonia and abnormal findings on chest Computed Tomography (CT). Interestingly, neurological symptoms, including headache, malaise, and loss of smell and taste, may affect some patients as initial manifestations, without any typical respiratory symptoms (8). Based upon a retrospective study in Wuhan, of 214 patients with confirmed COVID-19 infection, 36.4% had neurological manifestations that were categorized into CNS symptoms, Peripheral Nervous System (PNS) symptoms, and skeletal muscular symptoms. The most common features in patients with CNS symptoms were dizziness and headache. As such, hypogeusia and hyposmia were the most typical features for patients with PNS symptoms (8). These findings provide support for the susceptibility of the CNS to COVID-19, which can induce neurological diseases.

3. Evidence for the Involvement of CNS in COVID-19 Patients

As mentioned earlier, the neuroinvasive potential of COVID-19 has been confirmed in a more recent retrospective study (8). Consistent with this, another study demonstrating the capability of COVID-19 to cause nervous system damage showed that more than one-third of patients exhibited various neurological symptoms, including CNS symptoms (dizziness, headache, confusion, agitation, acute cerebrovascular disease, ataxia, and epilepsy) and PNS symptoms (taste impairment, smell impairment, vision impairment, and neuralgia). In general, patients with CNS manifestation mostly complain about headaches, dizziness, and impaired perception of taste and smell (6, 12, 13).

Of note, the nervous system impairments are more frequent in patients with severe infection, manifested as ischaemic stroke and intracranial hemorrhage (14, 15). In March 2019, Moriguchi et al. reported that COVID-19 caused viral encephalitis by invading the CNS, which was confirmed by detecting SARS-CoV-2RNA in the cerebrospinal fluid of the infected patient (16). More interestingly, a recent case study reported the neuroinvasive potential of COVID-19 in a 28-day-old neonate with neurological manifestations. In this study, the authors recommended the screening of infants aged less than three months with a fever of unknown origin for COVID-19 infection (17).

4. Possible Neuroinvasive Mechanisms of COVID-19

4.1. Possible Mechanisms of COVID-19 Leading to Neurological Infection

Some viruses are neurotropic and can invade the nervous system and result in the activation of macrophages, microglia, and astrocytes in the CNS (18, 19). The pathology of severe viral infections is associated with the development of Systemic Inflammatory Response Syndrome (SIRS). SIRS can be abnormally triggered by severe pneumonia induced by CoVs infection (20). In support of this, a previous study has suggested early anti-inflammatory interventions to effectively prevent immune damage and reduce the risk of injury in the nervous system in patients with COVID-19 (21). Furthermore, both SARS-CoV and SARS-CoV-2have been accompanied by a high mortality rate, mainly due to multiple organ failure (MOF) as a result of virus-induced SIRS or SIRS-like immune disorders (22, 23). Added to this, interleukin (IL)-6, an important member of the cytokine storm, is positively correlated with the severity of COVID-19 symptoms in patients (24). The same findings have been documented in another study, showing hypercytokinemia in COVID-19 patients (25).

Furthermore, the potential of CoVs to infect macrophages, microglia, and astrocytes in the CNS is of importance. These viruses have been known to have the ability to activate glial cells and induce proinflammatory cytokine production (26). This is further confirmed by an in vitro study that identified the increased levels of inflammatory factors, including IL-6, IL-12, IL-15, and TNF-α in primary glial cells after infection with CoVs (27). Given a high similarity between SARS-CoV-2and SARS-CoV, careful consideration of neurological signs, previously reported for other CoVs, is of significance, especially for elderly patients with COVID-19 who are more susceptible to neurological complications (Figure 1).

4.2. Possible Mechanisms of COVID-19 Leading to Encephalopathy

Generally, many viruses can lead to deleterious damages in the CNS, including severe encephalopathy, toxic encephalopathy, and severe acute demyelinating lesions (28, 29). There are many possible pathways for COVID-19 to access the CNS, which are completely discussed here. Of note, the COVID-19 virus might use one or a combination of several pathways to infiltrate into the CNS. Undoubtedly, the elucidation of the potential mechanisms involved in neurological damage following COVID-19 infection will help to better fight this pandemic.

A recent study has detected COVID-19 in the cerebrospinal fluid of an infected patient, associated with neurological manifestations such as seizure, suggesting that

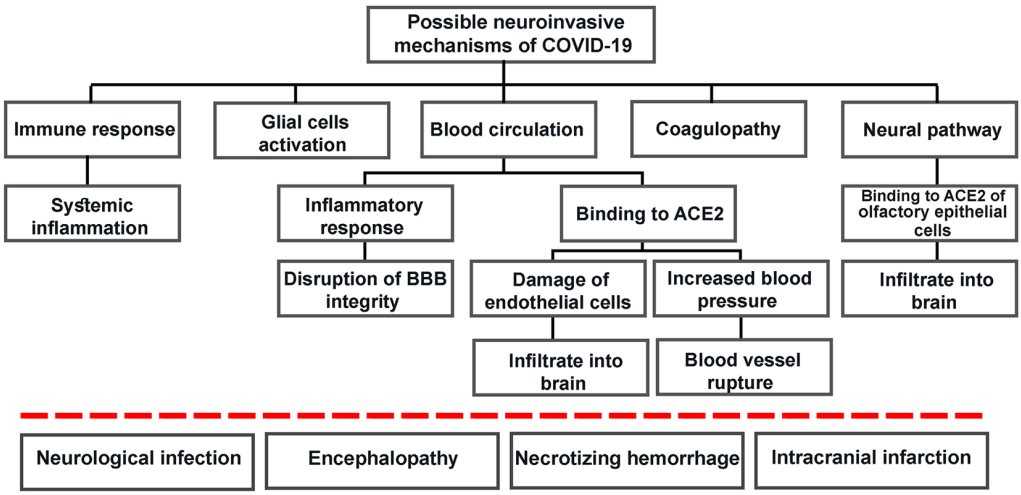

Figure 1. Possible neuroinvasive mechanisms of COVID-19. ACE2: Angiotensin-converting enzyme 2, BBB: blood-brain barrier

the virus can directly invade the nervous system and cause neurological damage (16). Added to this, other recent case reports have demonstrated the presence of encephalopathy in patients with severe COVID-19 in the absence of CSF viral detection, which might be due to the low viral load in the CNS (30, 31).

A possible mechanism, which may provide a route for viruses to enter the CNS, is blood circulation. As a consequence of inflammatory response induced by viral infections, elevated cytokine production in the body can result in the disruption of the blood-brain barrier integrity and eventually facilitate the entry of the virus into the brain and lead to viral encephalopathy. This possibility becomes more likely, as a subgroup of cases diagnosed with COVID-19 has been associated with cytokine storm syndrome (21, 25). Due to the limited available data, however, further studies are required to support this mechanism.

In addition, another possible mechanism can be the presence of the COVID-19 virus in the systemic circulation, which significantly enables it to pass into the cerebral circulation. This pathway can be explained by the presence of the low blood flow rate within microcirculation, which could be one of the factors facilitating the interplay of the COVID-19 virus s-protein with ACE2 expressed in the capillary endothelium. Finally, the virus can access the brain via the proliferation of viral particles in the capillary endothelium and damage to the endothelial lining. Meanwhile, in the milieu of the neuronal tissue, viruses can bind to ACE2 expressed in neurons and initiate a cycle of viral budding, which can induce neuronal injury without considerable inflammation (32). In addition, the binding to ACE2 can result in an abnormal increase in blood pressure and eventually elevate the risk of a cerebral hemorrhage, which can lead to serious consequences in patients with COVID-19 infection (15).

The neuronal pathway is another postulated mechanism that can be proposed for COVID-19 infiltration into the CNS. As mentioned earlier, the disruption of olfaction and taste perception is demonstrated to be one of the earliest symptoms in patients infected with COVID-19 (33). In the nasal cavity, there are a huge number of olfactory receptor neurons located in the olfactory epithelium, which are responsible for the transmit of olfactory information toward the brain (34). Indeed, olfactory epithelial cells in the nasal cavity also express ACE2, which can be a possible mechanism for anosmia in patients with COVID-19. Additionally, the anatomical structure of olfactory nerves in the nasal cavity has made it an exclusive channel between the nasal epithelium and the CNS (35). As a result, COVID-19 can infiltrate into the brain in the early stages of infection via the olfactory tract and initiate inflammation and demyelinating reaction. This mechanism has been extensively explained in a very recent review article (36).

4.3. Possible Mechanisms of COVID-19 Leading to Necrotizing Hemorrhagic Encephalopathy

The first reported case with acute necrotizing hemorrhagic encephalopathy was a female patient with COVID-19, who showed hemorrhagic lesions within the bilateral thalami, medial temporal lobes, and sub-insular regions in brain Magnetic Resonance Imaging (MRI) (37). Using brain CT, another case study also reported massive intracerebral

hemorrhage in the right hemisphere, as well as intraventricular and subarachnoid, in a 79-year-old patient diagnosed with COVID-19 (15).

As mentioned, COVID-19 can invade human cells mediated by the interplay between its S-proteins and ACE2 on cell surfaces (38). The main function of ACE2 is the degradation of angiotensin II, which finally results in regulating blood pressure (39). The COVID-19 virus may affect the expression and function of this protein, which can increase blood pressure and eventually lead to cerebral hemorrhage.

On the other hand, patients infected with COVID-19 usually suffer from coagulopathy and prolonged prothrombin time (6, 9). Therefore, it is plausible that this may be a factor in increasing the chance of cerebral hemorrhage. Additionally, due to the binding of SARS-CoV-2s-proteins to ACE2 expressed in the capillary endothelium, the virus may also disturb the blood-brain barrier permeability and infiltrate into the CNS by the disruption of the vascular system (40).

4.4. Possible Mechanisms of COVID-19 Leading to Intracranial Infarction

A recent retrospective study of COVID-19 patients has described acute stroke in four patients aged between 78 and 88, confirmed with brain CT (41). Similarly, another study also reported four cases of acute ischemic stroke in patients diagnosed with COVID-19. All four cases were aged between 45 and 77 years with increased blood pressure at the time of stroke. Interestingly, three of four patients had a history of hypertension with increased D-dimer levels without severe COVID-19 infection. The authors have suggested that ischemic cerebrovascular diseases may develop with COVID-19 infection regardless of the severity of the disease, and this event might be due to the increased serum levels of D-dimer and CRP, which may initiate thrombotic vascular injury (14). As a result, the increased levels of inflammatory markers might be a potential mechanism by which COVID-19 infection could potentiate the development of intracranial ischemia in infected patients.

5. Assessment and Management of Neurological Symptoms in COVID-19 Patients

COVID-19 is a highly contagious virus with an almost incubation period of 5 - 14 days (42). Currently, the gold standard laboratory test for confirming the diagnosis of COVID-19 infection in suspected cases is the nucleic acid amplification test. However, due to its low sensitivity, negative results do not rule out the possibility of infection, and repeated tests are often needed (43). Importantly, the manifestations of the disease are different among patients infected with COVID-19. As such, a majority of reports have predominantly addressed respiratory involvement as an early manifestation in patients. However, there is evidence that a limited number of patients have exhibited other disease manifestations, including neurological symptoms at the time of diagnosis, as completely discussed above (6, 8). Of note, neurological symptoms are more common in patients with severe infection, which can lead to ischemic stroke and cerebral hemorrhage and eventually raise the mortality rate (8, 14, 15). Moreover, hyperactivation of inflammatory markers and abnormal coagulation parameters that elevate the risk of cerebrovascular diseases are the main reasons for the clinical deterioration of the disease (44). In this context, it is important to mention that neurological manifestations are usually insignificant and non-specific at the early stages of COVID-19 infection, which may cause misdiagnosis and delay in patient management. Therefore, the careful consideration of medical history, physical examination, and imaging modality (45) is of importance to detect neurological symptoms for timely management and treatment of patients.

Based on a guideline by Jin et al., it is also useful to explore manifestations related to acute cerebrovascular diseases (high serum D-dimer level, severe thrombocytopenia, and cerebrovascular risk factors, including hypertension, diabetes, smoking, or previous stroke history), intracranial infection (headache, seizure, and disturbance in consciousness), and muscle damage (fatigue, limb ache, and elevated serum creatine kinase level). The guideline also includes a detailed discussion of precautions for neurologists, which is beyond the scope of this article (44).

6. Conclusion

In summary, emerging evidence has provided support for the susceptibility of the nervous system to COVID-19. Moreover, most patients infected with COVID-19 exhibit insignificant and non-specific neurological manifestations at the early stages of infection, which may cause misdiagnosis and delay in patient management. Given the limited available literature regarding the neurological presentations of COVID-19 in infected patients, further research is required to clarify the neurobiology and long-term neurological consequences of the disease on the nervous system to ensure optimum and timely management of patients.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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Footnotes

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