

# Coronavirus Disease 2019: Latest Data on Neuroinvasive Potential

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Received: 06 April 2020

Revised: 09 May 2020

Accepted: 06 June 2020

## What's Known

• COVID-19 is a pandemic whose neurological complications need clarification. Similar to other respiratory viruses, SARS-CoV-2 may enter the central nervous system via the hematogenous or neuronal route. While facing patients with any neurological markers, medical services suppliers should consider SARS-CoV-2 as a differential diagnosis to avoid misdiagnosis.

## What's New

• There isn't any worldwide significant data about neurological manifestation and complications of COVID-19 virus. We herein provide an update on the neurological pathogenesis and manifestations of coronaviruses and briefly discuss the latest findings on SARS-CoV-2 neuroinfection.

## Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic infection. Similar to other respiratory viruses, severe acute respiratory syndrome coronavirus (SARS-CoV-2) may enter the brain via the hematogenous or neuronal route; however, only a few reports are available on the neurological complications of COVID-19. Encephalopathy is a significant neurological complication of COVID-19. We herein present an update on the virology, neurological pathogenesis, and neuroinvasive potential of coronaviruses and briefly discuss the latest findings on SARS-CoV-2 neuroinfection. The reports thus far indicate that the access of SARS-CoV into host cells is bolstered chiefly by a cellular receptor, angiotensin-converting enzyme 2, and that SARS-CoV-2 may induce some neurological manifestations via direct or indirect mechanisms. Further research is required to shed sufficient light on the impact on the central nervous system and altered mental status in patients with COVID-19. Indeed, a better understanding of the pathways of SARS-CoV-2 neuroinvasion would further clarify the neurological pathogenesis and manifestations of coronaviruses and enhance the management and treatment of this group of patients. In the current epidemic era of COVID-19, health care staff should strongly become aware of SARS-CoV-2 infection as an essential diagnosis to get away misdiagnosis and prevention of transmission.

Please cite this article as: Haddadi K, Asadian L. Coronavirus Disease 2019: Latest Data on Neuroinvasive Potential. *Iran J Med Sci.* 2020;45(5):325-332. doi: 10.30476/ijms.2020.85980.1561.

**Keywords** • COVID-19 • Infections • Neurological manifestations • Coronavirus

## Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2), a novel coronavirus, originated in China in December 2019 and rapidly progressed into an epidemic infection, such that the World Health Organization (WHO) termed this calamitous virus "coronavirus disease 2019 (COVID-19)".<sup>1-3</sup> The majority of the early investigations focused on how SARS-CoV-2 attacks the respiratory system and elicits typical symptoms in most patients; nonetheless, new research disturbingly indicates that SARS-CoV-2 can also attack the central nervous system (CNS) in a variety of ways and even cause long-term damage or death.<sup>4</sup>

Neurological complications in COVID-19 infection have yet to be sufficiently elucidated. Patients with such complications may present with changes in their level of consciousness (e.g., acute encephalopathy). Acute infections increase the risk of altered mental status, especially in elderly patients with chronic medical illnesses.<sup>1-6</sup>

We herein present an update on the neurological pathogenesis and manifestations of Coronaviruses (CoVs) and briefly discuss the latest findings on SARS-CoV-2 neuroinfection in the limited literature.

#### *Viral Infections of the Central Nervous System*

Previous research shows that the central nervous system (CNS) is not immune to infection-induced changes, be they acute or latent. A wide spectrum of viruses attack the CNS of humans by infecting different specific cells such as neurons and, thus, produce neural diseases.<sup>7</sup> In clinical practice, however, a precise evaluation of the incidence of viral infections poses a challenge. By way of example, viral presence can be detected only in up to 30 cases out of 100 000 cases in the most prevalent viruses known to induce encephalitis (i.e., herpes viruses, arboviruses, and enteroviruses).<sup>8</sup>

Some researchers have posited that the clinical picture of viral infections is often nonspecific and needs the clinician to consider various diagnoses,<sup>7</sup> the most significant of which are meningitis, which produces such typical symptoms as fever, neck stiffness, and photophobia; encephalitis, whose signs and symptoms can be nonexistent but may cause confusion, speech disorders, and unusual activities; focal neurological deficits such as hemiparesis and paralysis; syndromes of movement disorders; and seizure.<sup>9</sup> Accordingly, the classification of the viral etiology of a neurological condition requires a thorough history taking and physical examination of the patient.<sup>9-12</sup>

#### *Virology*

##### *Coronaviruses*

CoVs are enveloped single-stranded Ribonucleic acid (RNA) viruses<sup>13-15</sup> that belong to the *Coronaviridae* family.<sup>16</sup> Human pathogenic CoVs comprise HCoV-229E, HCoV-OC43, HCoVHKU1, HCoV-NL63, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV),<sup>17-19</sup> all of which are capable of creating a variety of respiratory infections such as common colds, bronchiolitis, and pneumonia.<sup>18</sup> Numerous studies have also connected CoVs to CNS diseases such as acute disseminated encephalomyelitis and multiple sclerosis.<sup>20-22</sup>

##### *History of the Pathogenicity of the Neuroinfection of Coronaviruses*

CoVs are universal animal pathogens that can produce systemic and neurological illnesses in infected animals. CoVs lead to upper respiratory tract diseases<sup>23</sup> and are associated with

gastroenteritis<sup>24</sup> in humans. There are, however, two reports that posit a relationship between CoVs and human demyelinating disease. In one of these reports, the coronavirus was separated from the brains of two patients with multiple sclerosis patients.<sup>25</sup> The other report was on the observation of the coronavirus via electron microscopy in the brain immunocytes of a patient with multiple sclerosis.<sup>26</sup>

An article published in 1956 reported the intracerebral inoculation of a 10% homogenate of a mouse hepatitis virus (MHV) JHM-infected mouse brain into rhesus monkeys (*Macaca mulatta*) induced the acute manifestations of panencephalitis.<sup>27</sup>

##### *Immunity of the Central Nervous System*

Immune responses mediated by T lymphocytes in the CNS can be both beneficial in that they can clear inflammation mediators and harmful in that they may destroy neural tissues and activate autoimmunity and glial cells. The CNS responds swiftly to coronavirus involvement by recruiting the chemokine mediators of specific T cells. The detection of antigens expressed by the major histocompatibility complex (MHC) is vital in triggering antigen-specific T cells. However, extensive T-cell stimulation and self-antigen stimulation can finally produce disorders such as demyelination. Some mediators such as interferon regulatory factor 7 (IFN-7) may exert undesirable effects by employing macrophages and inducing the excessive secretion of astrocyte chemokines.<sup>28-30</sup>

Dissimilar to the cytolytic mechanisms expressed in acute infection, the immunity induced by the nonlytic humoral pathway succeeds in controlling infectious viruses through persistence. The current data appear to confirm CNS infection by SARS-CoV.<sup>31</sup>

##### *Cytokines*

Some investigations have reported high serum levels of interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein-1 (MCP-1) in patients with SARS-CoV or MERS-CoV.<sup>32, 33</sup> Some other studies have demonstrated considerable accumulation of IL-6, IL-8, and MCP-1 in the cerebrospinal fluid (CSF) of patients with the CoV infection of the CNS. IL-6 has both neurotrophic and neuroprotective properties and can increase the permeability of the blood-brain barrier.<sup>34</sup> A high level of IL-6 causes advanced neurological disorders.<sup>35</sup> A study in Japan on experimental mouse encephalitis verified that IL-8 played a vital role in inflammatory responses such as injury to the brain.<sup>36</sup> MCP-1 is a chemokine that can recruit the migration of

monocytes across the blood-brain barrier and invite inflammatory cells into the CNS. What ensues is the entry of virus-infected cells, an increased inflammatory response, and injury to the brain, particularly encephalitis.<sup>37,38</sup>

#### *SARS-CoV-2 Infection (the Novel COVID-19 Virus)*

The existing data show that the newly disseminated coronavirus (SARS-CoV-2) shares similar pathogenesis with SARS-CoV and MERS-CoV in the induction of pneumonia. SARS-CoV-2 uses a similar receptor to enter the human host cells.<sup>39-41</sup> Increasing evidence indicates that neurotropism is an important feature of CoVs. Consequently, it is crucial to understand whether SARS-CoV-2 can increase entrance to the CNS and induce neuronal damage, resulting in acute respiratory distress and death.<sup>42-44</sup> This neuroinvasive capability of CoVs has been recognized very nearly for all CoVs such as SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-OC43, as well as mouse hepatitis virus and porcine hepatitis E.<sup>45-47</sup>

#### *Neuroinvasive Potential of SARS-CoV-2 (Last Update)*

The particular pathway by which SARS-CoV or MERS-CoV arrives in the CNS has yet to be determined. Nevertheless, the lymphatic or hematogenous route appears to be likely, particularly in the primary stage of the infection, when almost no particle of the virus has thus far been identified in non-neuronal cells.<sup>31-33</sup> Growing evidence indicates that CoVs can reach the CNS after attacking peripheral nerve elements.<sup>44-46</sup>

In the years 2002 and 2003, some investigations reported the presence of SARS-CoV elements in the CNS, especially in the brain neuron cells.<sup>31, 48, 49</sup> Further studies afterward demonstrated that both SARS-CoV and MERS-CoV might intranasally, perhaps by way of the olfactory nerves, enter the brain and swiftly spread to some particular brain regions such as the brainstem and the thalamus. Amongst these areas, the brainstem has been verified to be severely infected by these viruses.<sup>50-52</sup>

The access of SARS-CoV into host cells is supported mostly by a cellular receptor, angiotensin-converting enzyme 2 (ACE2), which is expressed in the human respiratory system, small intestine, and kidney cells. Conversely, the existence of this enzyme uniquely is not adequate to make host cells vulnerable to infection.<sup>53-55</sup>

SARS-CoV-2 also has comparable potential. An epidemiological study on COVID-19 informed that the normal time from the first warning sign

to dyspnea was five days, to hospital admission was 7 days and to the intensive care unit (ICU) was eight days. Consequently, the latency phase could be enough for the virus to entree and demolish the medulla oblongata. Previous studies have also reported that some patients infected with SARS-CoV-2 showed neurological symptoms such as headache, ataxia, and convulsion.<sup>6, 56, 57</sup>

In a recent study on 214 patients with COVID-19, Mao and others<sup>6</sup> found that almost 88% of the patients with severe infection exhibited neurological signs such as acute cerebrovascular disease and altered mental status. Hence, awareness of the potential neuroinvasion can have guiding importance for the management of COVID-19-induced respiratory catastrophes.

Therefore, similar to more respiratory viruses, SARS-COV-2 can go into the brain through blood or neuronal systems. The presence of hyposmia in some patients supports the notion that the virus may enter the CNS via the neuronal pathway. There has been a report of the identification of the SARS-CoV nucleic acid in the CSF and brain tissue of patients with COVID-19.<sup>4</sup>

On March 4, 2020, Jingyuan<sup>5</sup> described a middle age patient with pneumonia in whose CSF SARS-CoV-2 was identified by genetic sequencing. The report also stated that despite the presence of signs and related to central nervous system damage, but brain imaging failed to expose any abnormalities and biochemical tests were normal for the CSF. Fortunately, however, the diagnostic test on the cerebrospinal fluid of the patient showing the existence of the SARS-CoV-2 coronavirus, and treatment for viral encephalitis was commenced.

On March 21, 2020, Filatov and others<sup>1</sup> described a 74-year-old man with respiratory disease, convulsion, altered mental status, and confusion who was diagnosed with COVID-19. The patient, however, exhibited no CSF evidence of CNS infection. The authors recommended awareness concerning the manifestations of encephalopathy in patients in the acute phase of COVID-19.

In a review published on February 27, 2020, Yan-Chao and colleagues<sup>57</sup> of Jilin University in China concluded that SARS-CoV-2 could contaminate nerve cells, chiefly neurons in the medulla oblongata (part of the brainstem that functions as the control center for the heart and the lungs). The injury could be related to acute respiratory failure in patients with COVID-19.

Indeed, while the bulk of research conducted and published thus far has focused on the mechanisms whereby SARS-CoV-2 targets the

respiratory system, more recent investigations have reported disconcerting evidence of the entrance of this new coronavirus into the CNS via different ways, resulting in significant damage to this system or even death due to its infection. Some investigators in China reported that more than 30% of their 214 patients with COVID-19 presented with neurological signs and symptoms; they, therefore, concluded that SARS-CoV-2 might attack the CNS through blood or retrograde neuronal routes, causing the destruction of the CNS.<sup>6</sup>

Most recently, we described a female patient who referred with exclusive manifestations. Our patient had altered mental status, the involvement of Brain basal ganglia, most probably due to COVID-19. She presented with respiratory manifestations and computed tomography scan-confirmed lung involvement typically matched by COVID-19 infection. We successfully treated her with routine anti-coronavirus drugs. What all the aforementioned cases indicate is that COVID-19 may have different types of CNS involvement that should be considered.<sup>5</sup>

There have also been reports of low lymphocyte counts in patients with COVID-19 who had neurological manifestations by comparison with patients with COVID-19 who had no such manifestations, which hints at the possibility that patients with CNS involvement may have various degrees of COVID-19-induced immunosuppression effects, particularly in the severe phase of the disease. A study reported high D-dimer levels in severe COVID-19 in comparison with non-severe COVID-19, indicating that the prevalence of cerebrovascular diseases may be higher in severely ill patients.<sup>6</sup>

#### *Muscle Involvement in COVID-19*

The latest reports on COVID-19 indicate the high incidence of muscle symptoms.<sup>2</sup> Moreover, creatine kinase and lactate dehydrogenase levels have been reported to be higher in patients with severe COVID-19 than in those with non-severe COVID-19, which could be correlated with the presence of ACE2 in skeletal muscles.<sup>56</sup> Consequently, whether SARS-CoV-2 infects muscle cells by binding to ACE2 receptors needs further research. It is also deserving of note that significantly elevated pro-inflammatory cytokines in serum can produce muscle injury.<sup>56</sup>

#### *Other Rare Complications*

**Stroke:** In some new articles, the incidence rate of ischemic stroke in patients with COVID-19 is up to 2.5%.<sup>58</sup> There are also reports regarding a relationship between inflammation and resultant coagulopathy by IL-6 and

fibrinogen due to damage to the lung alveoli.<sup>59</sup> The pathophysiology of the prothrombotic state subsequent to viral infections has been widely recognized. Patients' susceptibility to coagulopathy and thrombotic events can be explained by prolonged stays in intensive care units and disabilities.<sup>59, 60</sup>

**Guillain-Barré syndrome:** Some reports are indicating that this syndrome could be one of the considerable neurological complications of SARS-CoV-2.<sup>60</sup> The most likely mechanism is that antibodies against some surface glycoproteins are expressed against foreign antigens that also respond to the parallel native protein structure on the neurons. Nevertheless, the lack of relevant data and the complexity of establishing a causal relationship between a single pathogen and the syndrome make it extremely difficult to assess the robustness of the reported evidence.<sup>60</sup>

**Cerebrospinal fluid:** As yet, there is no specific CSF analysis feature in COVID-19 infection with neurological manifestations (especially encephalopathy), and the reported results thus far have been normal. Still, diagnostic tests on the CSF of patients may be essential to the diagnosis of COVID-19 neuroinfection.<sup>1, 5</sup>

## Discussion

New data analyses on COVID-19 indicate a noticeable incidence of neurological disorders, especially in more severe infection. The neurological disorders in COVID-19 may constitute a neurological tableau of a direct viral infection, neurological sequelae after the resolution of the infection, and infection in patients with chronic neurological diseases, not least those who require immune-suppressive medications (e.g., multiple sclerosis).<sup>6</sup> In light of the reported findings, the neurological signs and symptoms of SARS-CoV-2 neuroinfection may indicate the involvement of the CNS, creating such symptoms as headache, altered mental status, and epilepsy; the peripheral nervous system, creating such significant symptoms as hyposmia; and the skeletal muscles.<sup>6</sup>

## Conclusion

Based on the findings presented here, it can be concluded that similar to other respiratory viruses, SARS-COV-2 may enter the brain via the hematogenous or neuronal route. Hyposmia may be deemed evidence of the neuroinvasion capability of SARS-COV-2 via the olfactory route. Indeed, what the ACE2 theory posits is that SARS-CoV-2 may be responsible for some

neurological manifestations. In the current epidemic era of COVID-19, it is highly advisable that healthcare workers take into account SARS-CoV-2 infection as a differential diagnosis in patients presenting with any neurological indicators to avoid misdiagnosis and the transmission of this contagious infection. The ACE2 theory indicates that SARS-CoV-2 may induce some neurological manifestations via direct or indirect mechanisms.

Finally, gaining an insight into the pathways of SARS-CoV-2 neuroinvasion would further clarify the neurological pathogenesis and manifestations of CoVs and enhance the management and treatment of this group of patients.

### Acknowledgment

We wish to dedicate this study to all our colleagues and volunteers that work indefatigably against COVID-19, especially those in the northern Iranian province of Mazandaran. Many thanks are also due to all patients who suffered this contagious infection.

**Conflict of Interest:** None declared.

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