

# Looking ahead

## The risk of neurologic complications due to COVID-19

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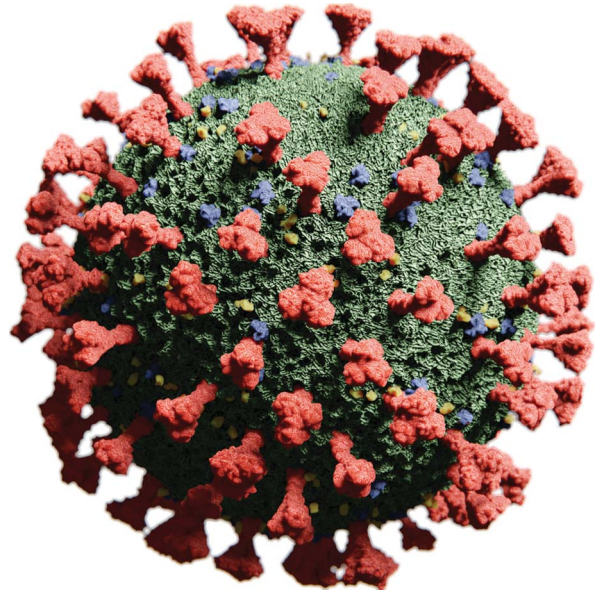
*Neurology: Clinical Practice* August 2020 vol. 10 no. 4 371-374 doi:10.1212/CPJ.0000000000000836

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### Abstract

The rapid spread of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has become a public health emergency of international concern. The outbreak was characterized as a pandemic by the World Health Organization (WHO) in March 2020. The most characteristic symptom of patients with COVID-19 is respiratory distress. Some patients may also show neurologic signs and symptoms ranging from headache, nausea, vomiting, and confusion to anosmia, ageusia, encephalitis, and stroke. Coronaviruses are known pathogens with neuroinvasive potential. There is increasing evidence that coronavirus infections are not always confined to the respiratory tract. CNS involvement can occur in susceptible individuals and may contribute overall morbidity and mortality in the acute setting. In addition, post-infectious, immune-mediated complications in the convalescent period are possible. Awareness and recognition of neurologic manifestations is essential to guide therapeutic decision-making because the current outbreak continues to unfold.



### Virology and taxonomy

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the broad family of coronaviruses.<sup>1,2</sup> It is an enveloped, positive sense, single-stranded RNA (+ssRNA) virus with a diameter of approximately 60–140 nm.<sup>3</sup> The viral envelope consists of a lipid bilayer with 4 structural proteins known as S (spike), E (envelope), M (membrane), and N (nucleocapsid).<sup>2</sup> Interaction between the spike protein and host cell receptor is essential for virulence and infectivity.<sup>4</sup> Similar to severe acute respiratory syndrome coronavirus (SARS-CoV)—the causative agent of the SARS global outbreak in 2003—and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is a member of the genus *Betacoronavirus* ( $\beta$ CoV).<sup>5</sup>

Genomic sequence analyses of SARS-CoV-2 have shown 82% identity with SARS-CoV<sup>6</sup> and an estimated mutation rate of approximately  $10^{-3}$  substitutions per site per year,<sup>7</sup> similar to other ssRNA viruses. Although a mutation in the spike protein is the likely culprit for the recent introduction of SARS-CoV-2 into the human population, sequence variation among various isolates remains low, and a few mutation “hot spots” have now been described.<sup>8</sup> These advances should help facilitate vaccine design, clinical monitoring, and management of Coronavirus disease 2019 (COVID-19).

The neuroinvasive nature of human coronaviruses has been previously described, and neurotoxicity may occur because of indirect, direct, and postinfectious complications.<sup>9</sup>

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).

## Indirect neurologic complications

Coronaviruses generally cause respiratory and enteric diseases in animals and humans.<sup>2</sup> In a report of 44,500 confirmed COVID-19 patients by the Chinese Center for Disease Control and Prevention, 81% of cases consisted of mild pneumonia, 14% were characterized by more severe diseases, including dyspnea and hypoxia, and 5% had respiratory failure, shock, or multiorgan dysfunction.<sup>10</sup> Sepsis, heart failure, and septic shock are among the most frequently reported systemic complications of COVID-19,<sup>11</sup> and extrapulmonary involvement of SARS-CoV-2 may induce neurologic signs and symptoms.

A recent report of 99 COVID-19 patients in Wuhan, China, described the presence of neurologic manifestations, including confusion (9%) and headache (8%).<sup>5</sup> In a different report of 214 COVID-19 patients, 36.4% were found to have neurologic manifestations at presentation, including headache, nausea, vomiting, impaired consciousness, ataxia, acute cerebrovascular disease, and seizures.<sup>12</sup> Secondary neurologic manifestations of COVID-19 are believed to result from the widespread dysregulation of homeostasis due to pulmonary, renal, hepatic, and cardiovascular injuries.<sup>13</sup> In addition, direct and indirect cardiotoxicities secondary to excessive systemic proinflammatory stimulation (cytokine storm), hypercoagulability, and direct myocardial invasion are associated with myocardial infarction, heart failure, and arrhythmias, which are the important risk factors for stroke.<sup>11</sup>

## Direct neurologic complications

In previous SARS-CoV infections, *postmortem* studies have reported the presence of viral RNA within brain tissue of the affected individuals.<sup>14</sup> Acutely ill patients with SARS-CoV have also demonstrated the presence of the virus in the CSF.<sup>13</sup> Experimental animal studies using transgenic mice have further revealed that after the intranasal administration of SARS-CoV, the virus can enter the brain, and thereafter, it may spread to specific areas of the CNS, including the thalamus and the brainstem.<sup>15</sup> In addition, cases of human coronavirus (HCoV)-related meningitis, encephalitis, and acute flaccid paralysis have been reported over the years.<sup>9</sup>

Similar to SARS-CoV, SARS-CoV-2 seems to enter human host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of epithelial cells in the lung, intestine, kidney, and blood vessels.<sup>13,16</sup> The exact mechanism by which SARS-CoV enters the CNS remains unclear but may involve disruption of the nasal epithelium and entry via the olfactory bulb with subsequent retrograde transsynaptic spread.<sup>9</sup> Interestingly, evidence of neuronal expression of the ACE2 receptor has recently emerged from human protein databases,<sup>17</sup> but a clear role for this receptor in HCoV entry into the CNS has not been established. A recent report describing the ability of HCoV to induce direct

neuronal injury within brainstem cardiorespiratory centers in experimental animal models<sup>2</sup> has raised concern that SARS-CoV-2 may be partially responsible for the acute respiratory failure reported in patients with COVID-19.

In addition, an association between COVID-19 and early onset olfactory and gustatory dysfunction has been reported recently.<sup>18</sup> The American Academy of Otolaryngology proposed that anosmia, hyposmia, and dysgeusia should be added to the list of COVID-19 screening symptoms and urged precautionary isolation for individuals with these symptoms, even in the absence of respiratory disease.<sup>18</sup> Although changes in smell and taste perception are known complications of a range of viral infections, these observations raise the question of whether these changes arise from secondary inflammatory processes or are due to SARS-CoV-2–related dysfunction in olfactory and gustatory processing mechanisms. Of note, ACE2 is also expressed in microvillar and Bowman gland cells,<sup>19</sup> but a direct pathogenic role for SARS-CoV-2–related olfactory epithelium damage and CNS entry has not been established. A genetic predisposition for an increased risk of COVID-19–related neurologic complications, which may be partially due to ACE2 polymorphisms linked to these conditions in previous studies, should be further investigated.

## Postinfectious neurologic complications

After the acute phase of the infection, the presence and persistence of human coronaviruses within the CNS may lead to misdirected host immune responses, which could be associated with autoimmune inflammatory and demyelinating syndromes in susceptible individuals.<sup>9</sup> In support of this hypothesis, the presence of HCoV RNA in the CSF of patients with acute disseminated encephalomyelitis<sup>20</sup> and multiple sclerosis (MS)<sup>21</sup> has been reported. HCoV infections have also been associated with other postinfectious syndromes, including encephalitis and Guillain-Barré syndrome.<sup>22</sup> Proposed pathogenic mechanisms include molecular mimicry between HCoV and myelin basic protein<sup>23</sup> and direct invasion of leukocytes and other immune cells.<sup>9</sup> Notably, dysregulation of the ACE2 receptor has also been implicated in the development of experimental autoimmune encephalomyelitis, a murine disease model that resembles multiple sclerosis.<sup>17</sup>

## Immunopathogenesis

The structural and phylogenetic similarities between SARS-CoV-2 and SARS-CoV suggest that the known pathophysiologic mechanisms for related human coronaviruses are likely applicable to SARS-CoV-2. After invasion of lung epithelium, SARS-CoV directly infects T cells and macrophages, contributing to lymphopenia with reduced CD4<sup>+</sup> and CD8<sup>+</sup> cell counts and dysregulation of normal adaptive immune responses.<sup>4</sup> Excessive

production of proinflammatory cytokines including interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-10, and tumor necrosis factor-alpha (TNF- $\alpha$ ), with subsequent downregulation of anti-inflammatory cytokines such as interferon gamma (IFN- $\gamma$ ), are believed to contribute to excessive inflammation and activation of proapoptotic pathways.<sup>24</sup>

In some cases, adaptive immune responses might become directed against host epitopes, resulting in postinfectious autoimmune reactions that prolong the inflammatory phase and induce tissue destruction even after the virus has been cleared.<sup>9</sup> Data from experimental animal studies suggest that antibodies might also contribute to immunopathogenesis because increased uptake of coronavirus by macrophages can lead to macrophage activation and secretion of cytokines and other chemokines.<sup>4</sup> In addition, coronavirus-specific T cells and antibodies have been shown to activate macrophages, resulting in their migration into the CNS and, ultimately, in demyelination.<sup>25</sup>

## Immunotherapies

The assumption that immunocompromised patients could be at increased risk for severe disease and mortality from COVID-19, presumably because of a lack of a robust immune response, has been a matter of recent debate. A recent report by Liang et al.<sup>26</sup> suggested that cancer patients might be at increased risk of infection and have a poorer prognosis than individuals without cancer. Conversely, it has also been suggested that immunosuppressive states may actually help blunt hyperinflammatory responses in patients with COVID-19,<sup>27</sup> and a multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blocker approved for the treatment of cytokine release syndrome) has been approved in China for patients with COVID-19 pneumonia and elevated IL-6 (ChiCTR2000029765).<sup>28</sup> However, these assumptions are largely based on the available information from small cohorts and current evidence remains insufficient to explain an association between immunosuppressed states and the risk for COVID-19.

Nevertheless, these observations raise important questions regarding the safety of immune-modulating therapies in patients with multiple sclerosis, myasthenia gravis, and other neuroimmune disorders. In conjunction with the National Medical Advisory Committee, the National Multiple Sclerosis Society (NMSS) recently published recommendations regarding the use, continuation, and initiation of disease-modifying therapies (DMT).<sup>29</sup> The Association of British Neurologists (ABN) has also published general advice related to DMT use in patients with MS<sup>30</sup> and immunosuppressive drugs in other neuroimmunologic conditions.<sup>31</sup> However, these recommendations are largely based on medical expertise, and more organized data are currently needed to understand the true risk of DMT use in patients with MS, keeping in mind that immunosuppression in this

population presents distinct challenges that differ from other immunocompromised subtypes, including HIV and cancer, and data obtained from these cohorts may not be applicable to multiple sclerosis and other neurologic conditions.

In light of the current lack of specific treatment, the US Food and Drug Administration (FDA) recently approved the use of COVID-19 convalescent plasma in patients with severe, life-threatening disease requiring mechanical ventilation or continuous positive airway pressure,<sup>32</sup> which has shown promising results in a small preliminary uncontrolled case series.<sup>33</sup> The use of this treatment modality is largely based on the premise that antibodies may be helpful in improving immune responses against SARS-CoV-2, but the potential risks of such therapies remain unknown. Novel therapies to combat the COVID-19 pandemic, including vaccines, should be designed to minimize pulmonary (and systemic) disease while optimizing an equilibrated anti-SARS-CoV-2 immune response because dysregulation of normal host immune responses could also lead to untoward consequences.

Taken together, neurotropism and neuropathogenic potential seem to be the common features of HCoV. As the full clinical spectrum of COVID-19 continues to be described, it is quite likely that SARS-CoV-2 possesses a similar potential for extrapulmonary pathology and CNS invasion. The putative role of ACE2 in the pathophysiology of COVID-19 has recently fueled concerns regarding the use of nonsteroidal anti-inflammatory drugs, such as ibuprofen, which are known to induce the upregulation of ACE2 and, in theory, may facilitate infection with COVID-19.<sup>16</sup> Based on these observations, it would be reasonable to speculate that treatment with these ACE2-stimulating drugs could similarly increase the risk for severe and fatal COVID-19 from CNS complications. Owing to the paucity of current medical literature describing the neuropathogenic potential of human coronaviruses, the number of COVID-19-related neurologic complications is likely underestimated. A cross-disciplinary perspective is essential in preparing for the potential consequences of the current pandemic to human health. Awareness of the risk for acute and postinfectious neurologic complications and their contribution to COVID-19-related morbidity and mortality can help guide therapeutic decision-making and allow for the delivery of individualized treatment because the number of reported cases continues to rise.

## Study funding

No targeted funding reported.

## Disclosure

The author reports no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).



## Publication history

Received by *Neurology: Clinical Practice* March 31, 2020. Accepted in final form April 6, 2020.

## Appendix Author

Name	Location	Contribution
<b>Carlos A. Pérez, MD</b>	University of Texas Health Science Center at Houston, Houston, TX	Drafting/revising the manuscript, data acquisition, study concept or design, and analysis or interpretation of data

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