How COVID-19 Affects the Brain

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As of April 9, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected 1,436,198 people and caused 85,522 deaths. By the time you read this, those numbers will have increased. As the numbers grow, more and more neurologic symptoms are being reported in COVID-19 patients. Neurologists, in turn, may increasingly find themselves involved in caring for patients with the novel virus.

COVID-19 may affect the nervous system via four potential mechanisms, which may overlap. The first is direct viral injury of nervous tissue, such as occurs with herpes simplex encephalitis. Although there are some suggestive case reports, there is no definite proof that the SARS-CoV-2 virus directly damages the central nervous system (CNS).

The second type of injury results from an excessive immune response in the form of a "cytokine storm." Cytokines can cross the blood-brain barrier and are associated with acute necrotizing encephalopathy. Only one case concurrent with COVID-19 has been reported.

The third mechanism of nervous tissue damage results from unintended host immune response effects after an acute infection. An example of this type of indirect CNS injury is Guillain-Barré syndrome (GBS). One case of GBS associated with COVID-19 has been reported, but the evidence for cause and effect is weak.

The fourth mechanism of indirect viral injury results from the effects of systemic illness. Neurologists are accustomed to seeing severely ill patients in the intensive care unit develop neurologic symptoms such as encephalopathy, critical illness myopathy, and neuropathy. Most cases of COVID-19-related neurologic complications appear to fall into this category.

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In February of this year, Guan and colleagues reported the clinical characteristics of SARS-CoV-2 infection in 1099 patients. Neurologic symptoms in patients with COVID-19 included headache (13.6%) and myalgias (14.9%). Only 5% required intensive care unit admission. On the basis of this large series, there seemed little reason to worry that SARS-CoV-2 might directly or indirectly attack the CNS or peripheral nervous system (PNS).

However, a separate, nearly simultaneous retrospective case series reported a high incidence of neurologic symptoms in 214 hospitalized patients with confirmed COVID-19 in Wuhan, China. Seventy-eight (36.4%) patients had CNS (24.8%), PNS (8.9%), or skeletal muscle symptoms (10.7%). The two most common CNS symptoms were dizziness (16.8%) and headache (13.1%), with acute cerebrovascular disease, ataxia, epilepsy, and impaired consciousness also reported. Severely ill patients were more likely to develop neurologic symptoms such as altered mental status, ischemic or hemorrhagic stroke, and muscle injury.

The most common PNS symptoms were hypogeusia (5.6%) and hyposmia (5.1%), with vision impairment and nerve pain also reported (because taste and smell are dependent upon cranial nerves, these would more accurately be considered deficits due to CNS injury). Neurologic involvement carried a poor prognosis.

The authors hypothesized that SARS-CoV-2 might enter the nervous system via the angiotensin-converting enzyme 2 (ACE2) functional receptor, which is present in glial cells, neurons, skeletal muscle, and other organs. Potential entry routes to the CNS include hematogenous spread and retrograde neuronal transmission through olfactory neurons in the cribriform plate.

They noted that studies of another member of the coronavirus family, SARS-CoV, indicate that direct brain entry is possible, and direct coronavirus spread to the medullary cardiorespiratory center may partially underlie COVID-19 respiratory failure. SARS-CoV nucleic acid has been found in the cerebrospinal fluid and brain tissue of patients infected with SARS-CoV, while invasion of the brain with SARS-CoV via the olfactory system in mice can also occur.

Felicia Chow, MD, MAS, a neuro-infectious disease expert at the University of California in San Francisco, is part of a team establishing an observational cohort of COVID-19 patients to learn more about its neurologic complications. Chow commented, "Some of the best evidence that the SARS-CoV-2 virus can target the nervous system is the finding of anosmia, which could be due to viral invasion of the olfactory bulb. But the loss of smell could also could be immune-

mediated due to antibodies and may not necessarily represent neurotropism."

Chow added, "It is also true that ACE receptors are present in neurons and glial cells, so theoretically, the coronavirus could directly enter the brain, but this is speculative. Researchers in Hong Kong have stated that the virus does infect neurons, but the data are not yet published. As of now, we don't know."

A review of 221 patients published in March echoed other review findings, revealing 13 patients (5.9%) with cerebrovascular disease. Eleven (5%) had an acute ischemic stroke, one had a cerebral venous sinus thrombosis (0.5%), and one a cerebral hemorrhage (0.5%). These patients were likely to be older with cardiovascular risk factors of hypertension or diabetes mellitus. Eleven of the 13 (85%) had severe SARS-CoV-2 infection. Increased inflammatory response and hypercoagulable state secondary to COVID-19 may have contributed to these events. Of the 13 patients, 5 died.

One patient with acute hemorrhagic necrotizing encephalopathy associated with COVID-19 has been described, possibly due to a cytokine storm, while a possible example of indirect viral nerve injury is a single case report of GBS associated with SARS-CoV-2 infection. However, this case was atypical as GBS occurred 1 week before the development of clinical symptoms rather than afterward. The authors concede that GBS in this setting may have been a coincidence. No postviral neurologic complications have yet been reported.

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Raymond Roos, MD, Marjorie and Robert E. Straus Professor of Neurology at the University of Chicago in Illinois, commented, "The main problem with COVID-19 cases has been a respiratory one. Sometimes patients can have confusion or a disturbed state of consciousness from the systemic involvement, especially if the oxygen level is low. In these cases, neurologists may be consulted to determine whether there is evidence of a primary neurologic problem and to provide guidance as to what tests should be carried out."

Roos added, "Evidence that these symptoms are from systemic problems is supported by the substantial number of patients who we see with similar symptoms from a systemic disease. The absence of focal neurologic signs, such as weakness of one side, suggests a systemic rather than a neurologic problem." Yet he acknowledges that we physicians, including neurologists, have relatively little experience with this virus. "It may be premature to be certain that we are not missing patients with a primary neurologic problem," he said, pointing out that the JHM strain of the mouse hepatitis virus can cause very significant neurologic disease.

Chow offered practical tips for the management of critically ill patients with COVID-19, suggesting that neurologists continue to employ conventional logic and tools. "If patients have neurologic signs and symptoms, then I would consider a lumbar puncture or neuroimaging. Just because the patient is positive for SARS-CoV-2 doesn't mean that they don't have a different etiology for their neurologic symptoms." She added that many patients with Alzheimer's or Parkinson's disease might be at risk for severe COVID-19 infection because they are elderly. "I would tell these patients that they are high-risk and should absolutely be staying home—the same advice I would give to someone on chemotherapy," she advised.

In theory, patients with multiple sclerosis treated with immunosuppressive drugs could be especially vulnerable to severe COVID-19 disease, but as Mount Sinai neurologist Stephen Krieger, MD, told Medscape, "Thankfully, there is...little evidence to date of increased infection susceptibility or risk for patients treated with disease-modifying therapies."

With respect to treatment, Chow opined, "At this point, there is no specific treatment even if we knew that the virus was neurotropic. If the virus is causing immune-mediated neural injury, theoretically, plasma exchange, IVIg, or steroids might be helpful. If it's direct viral injury, then you need an effective antiviral treatment, which we don't yet have."

Despite the wide variety of neurologic complications potentially associated with SARS-CoV-2 infection, it is still unclear whether these symptoms result from direct neural injury. Currently, it appears that most neurologic symptoms of COVID-19 are nonspecific and secondary to systemic illness. The literature contains only a single case of acute hemorrhagic necrotizing encephalopathy, while the patient with SARS-CoV-2–associated GBS is an atypical case.

For now, there is no convincing evidence that the SARS-CoV-2 virus directly affects the CNS or PNS in humans. As neurologists treat an

ever increasing number of COVID-19 patients, our understanding of the neurologic profile of SARS-CoV-2 infection will continue to evolve. Postinfection surveillance will be necessary to identify possible post-COVID neurologic syndromes.

Additional resource: The American Academy of Neurology has created an active COVID-19 resource center at AAN.com. A recent 20-minute YouTube video with Joseph E. Safdieh, MD, editor-in-chief of Neurology Today, addresses the impact of coronavirus on the practice of neurology.

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