

White Paper on the Neurologic Problems Associated with COVID-19 Infection

May 8, 2020

Since its introduction to the human population in or before December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), now termed COVID-19 virus, has resulted in a pandemic that has spread across the world resulting in millions of cases and hundreds of thousands of deaths with widely varying estimates of additional infection and death rates over time. COVID-19 is a novel virus which has been shown to be highly transmittable with both similarities to and differences in manifestation from other prior coronaviruses. Rightly, much attention has been focused on the hallmark presenting COVID-19 symptoms including but not limited to fever, shortness of breath, and cough with widely varying outcomes including respiratory failure. Rapidly emerging clinical and research findings have begun to document neurologic involvement resulting from direct and indirect effects of the infection and which have short- and long-term implications for patients. The purpose of this report is to provide current specific information on how COVID-19 impacts neurologic functioning and to help with the management of these problems.

It has been well documented that those infected with COVID-19 have vastly divergent symptom presentations ranging from those who are asymptomatic to those who do not survive. Patients diagnosed with COVID-19 have been found to experience a range of neurological symptoms. As has been the case with other viruses which cross the blood brain barrier, COVID-19 has been found to impact both the peripheral and central nervous structures and processes. Researchers have noted that patients with more severe cases of COVID-19 are more likely to develop neurological symptoms than patients who have a mild manifestation of infection. Symptoms of COVID-19 on the peripheral nervous system include gustatory impairment, anosmia (loss of smell), vision impairment and nerve pain. Central nervous system symptoms include disorientation, loss of consciousness, headache, delirium and coma. These symptoms may appear separately or collectively in patients diagnosed with COVID-19, and they are most commonly seen in patients who develop encephalopathy and/or cerebrovascular disease. Mao and colleagues (2020) found that 36% of patients with COVID-19 exhibited from mild to severe neurologic symptoms. Importantly, they also reported that those with severe disease courses, 45% of their study population exhibited significant neurologic sequela.

The etiology of neurologic sequela in COVID-19 is often difficult to determine as there are both direct and indirect factors that impact neurologic function and structure. Three processes are gaining attention as key contributors to neurologic manifestation including viral encephalitis,

infectious toxic encephalopathy, and acute cerebrovascular disease. Viral encephalitis is characterized by inflammatory lesions in the brain and common symptoms included headache, fever, vomiting, convulsions, and consciousness disorders. Through genome sequencing on cerebral spinal fluid of patients diagnosed with COVID-19, researchers have confirmed the presence of COVID-19 in cerebrospinal fluid and hypothesized that encephalitis may be a direct consequence of COVID-19 attack on the cells of the nervous system.

Patients with COVID-19 often suffer from severe hypoxia and viremia as well as metabolic disruption associated with diffuse organ involvement, any of which can result in infectious toxic encephalopathy. This condition is associated with cerebral edema without evidence of direct neuronal infection and inflammation, and its symptoms vary depending upon the severity of the case. Seriously affected patients may experience disorientation, loss of consciousness, coma, and paralysis, while more mild cases develop headaches, dysphoria, and delirium.

Acute cerebrovascular disease, both cerebral occlusion and hemorrhage has been increasingly noted in many prior studies as an unfortunate consequence of the infection. It has been well described in influenza, another coronavirus infection, that an overproduction of immune cells and/ or release of cytokines, increases the risk of these complications. Unfortunately, a similar overproduction of cytokine has been noted in COVID-19 although the frequency of occurrence is not known.

There are additional direct and indirect neurologic involvement which can have devastating impact. Not uncommonly, generalized symptoms such as dizziness and headache may result due to a variety of causes. A recent case study described the clinical course of a woman with active COVID-19 infection who developed Acute Necrotizing Encephalopathy (ANE). While ANE is typically described within the pediatric population, it is also known to occur in adults as a rare complication of viral infections. Characteristically, ANE features symmetric, multifocal lesions within the thalamus on CT imaging and MRI often shows internal hemorrhaging. This was the first reported case of COVID-19-associated acute necrotizing hemorrhagic encephalopathy..

Medical providers have also raised concerns that the use of mechanical ventilation in treating respiratory symptoms in patients diagnosed with COVID-19 may contribute to the development of neurocognitive impairment. Stretching of pulmonary alveoli, blood gas tension abnormalities, and cytokine presence in the lungs are critical mechanisms that possibly contribute to mechanical ventilation-related brain damage. Clinical relevance of alveolar stretching appears to cause production of various cerebral actors (cytokines, chemokines, microglia, immune system activation) that often lead to neuroinflammation as well as beta amyloid production, which is typically exhibited in Alzheimer's disease. Additionally, blood gas tension abnormalities, including hypoxia and hyperoxia, can persist during mechanical ventilation and lead to neuronal death, cerebral oxidative stress, and alterations in brain blood flow that may exacerbate brain damage. It is also important to note that hypoxia has been hypothesized to be a common cause of long-term cognitive impairment in patients with acute respiratory distress syndrome.

Primary attention with COVID-19 is rightly focused on respiratory features but it will also be important to consider neurologic consequences in a sizable minority of those with COVID-19, especially those who experience more severe disease courses. This includes both short- and long-term sequela and it is reasonable to expect that neurologically compromised COVID-19 survivors will need additional services and supports with some not being able to return to key areas of functioning. Epidemiological studies will play a critical role in determine the degree and nature of neurologic changes and resulting consequences. Rapid dissemination of information on neurologic sequela is imperative in order to allow that patients be properly screened for neurologic dysfunction and appropriate interventions be employed. Longitudinal research will elucidate the extent and nature of lasting deficits. The state of Iowa has an existing network resources to support individuals with brain injury and these partnerships will be critical in meeting the current and future needs of Iowans suffering lasting effects of COVID-19.

Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. Published online April 10, 2020. doi:10.1001/jamaneurol.2020.1127

Pleasure, S., Green, M, & Josephson, M. (2020) The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection Neurologists move to the front lines. *JAMA Neurol*. Published online April 10, 2020. Doi:10.1001/jamaneurol.2020.1065.

Poyiadji, N, Shahin, G, Noujaim, D, Stone, M, Patel, S, Griffith, B. (2020) COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*, Published online March 31,2020. <https://doi.org/10.1148/radiol.2020201187>

Wu, Y, Xu, X, Chen, Z, Duan, J, Hashimoto, K, Yang, L, Liu, C, & Yang, C. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, behavior, and immunity*, S0889-1591(20)30357-3. Advance online publication. <https://doi.org/10.1016/j.bbi.2020.03.031>

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