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## COVID-19-associated CNS Demyelinating Diseases

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Neurological manifestations of SARS-CoV-2 infection are increasingly being recognized. The most common neurologic symptoms include headache, anosmia, and dysgeusia, but patients may also develop other central nervous system (CNS) diseases. If we focus on the coronavirus family, there is clear evidence of its neurotropic character as demyelinating disease has been previously reported with MERS and SARS-CoV-1 (Dessau, 2001). However, data remains limited in terms of cases of CNS post-infectious demyelinating/inflammatory disease following COVID-19. Recent studies have shown that the novel coronavirus appears to cross the blood-brain barrier and cause acute or delayed CNS demyelination or axonal damage (Desforges, 2020). A variety of mechanisms have been postulated including virus-induced hypercoagulable or pro-inflammatory states, direct viral invasion of the CNS, and post-infectious immune-mediated processes.

The first radiologic description of neurologic complications due to SARS-CoV-2 infection was described by Poyiadji et al. with a case of acute necrotizing encephalopathy (ANE), probably related to virus-induced cytokine storm. For SARS CoV-2 infection, the pro-inflammatory state induced by the cytokine storm, mainly sustained by IL-1, IL-6, and TNF- $\alpha$ , may be responsible for the activation of glial cells with subsequent demyelination (Mehta, 2020). A possible alternative could be the production of antibodies against glial cells triggered by the virus, as a para-infectious or post-infectious phenomenon.

Coronaviruses have been associated with other demyelinating pathologies like acute or subacute disseminated encephalomyelitis (ADEM) in humans (Yeh, 2004). ADEM is a rare acute inflammatory demyelinating disease that may follow viral infections. The first case of COVID-19 associated ADEM was described in a 40-year-old woman (Zhang, 2020). Another case of ADEM was reported in a 54-year-old woman following COVID-19 disease. SARS-CoV-2 was not detected in the CSF probably because the neurological damage was sustained by a delayed immune response occurring after the viremia (Zanin, 2020). The first reported case of SARS-CoV-2 causing acute transverse myelitis was reported from Wuhan, China, where the outbreak first began, and the second case from Boston (Zhao 2020, Sarma 2020). Since then, a few cases from different parts of the world have also been reported.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the CNS. The cause of MS is so far unknown, but both genetic and environmental factors are considered important. Environmental factors, especially viruses, have been associated with the development of demyelinating disease, but no specific agent has yet been definitively linked to MS. For example, Epstein-Barr virus infection is considered an important risk factor for the development of MS (Donati, 2020). SARS-CoV-2 may play a role of infective trigger, similar to the one of Epstein Barr virus in MS. The presence of demyelination, as well as SARS virus particles and genome sequences, in the brain has been detected in autopsy studies (Zhang, 2003).

At Thomas Jefferson University Hospital, we recently described the first case of Neuromyelitis optica (NMO) potentially triggered by SARS-CoV-2 infection. NMO is a rare, inflammatory demyelinating disease of the CNS, predominantly affecting the optic nerves and spinal cord. NMO is diagnosed by the presence of at least 1 of 6 core clinical characteristics and detection of NMO/AQP4 IgG. The core clinical characteristics each implicate 1 of 6 CNS regions: optic nerve, spinal cord, area postrema of the dorsal medulla, brainstem, diencephalon, or cerebrum (Wingerchuk, 2015). Our patient met criteria for NMO based on the following 2 clinical characteristics: longitudinally extensive transverse myelitis (spinal cord lesion spanning greater than 3 segments) and area postrema syndrome (dorsal medullary lesion) in the setting of positive NMO/AQP-4 serum antibodies.

In all forms of demyelinating disease described above, causality remains difficult to prove, but the temporal relationship between SARS-CoV-2 infection and the onset/diagnosis of demyelinating event is compelling

for parainfectious phenomenon.

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