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Lessons from COVID-19 in Clinical Neurology

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COVID-19 has had a considerable impact on society. One negative impact of this disease is the neurological dysfunctions that can result from SARS-CoV-2 infection, in addition to respiratory problems. One in 20 patients with COVID-19 complains of neurological complications,[1] but whether COVID-19 provokes or triggers neurological problems remains unclear. There is a need for thorough research into the correlation between COVID-19 and neurological disorders. Before feasible research methods are set up, the only way to evaluate the causal relationship would be to carefully examine the temporal relationships between COVID-19 infection and neurological complications based on the accumulated clinical data. Since the COVID-19 outbreak, the *Journal of Clinical Neurology* (JCN) has published several reports related to COVID-19, including two original articles.

The first report in JCN was a case report of recurrent transient ischemic attack in a 47-year-old male with COVID-19 who did not have risk factors related to stroke.[2] He experienced transient symptoms with left-side weakness and amaurosis fugax at 5 days after being admitted to hospital due to COVID-19. Another case report was also a patient with ischemic stroke associated with endocarditis of unknown origin after COVID-19.[3] There have been increasing concerns regarding acute stroke related to COVID-19. Although this association remains controversial, clinical evidence for it is accumulating. A meta-analysis suggested a relatively high mortality rate and a considerable number of antiphospholipid-antibody-positive cases in acute ischemic stroke patients with COVID-19 infection.[4] A review article introduced angiotensin-converting enzyme-2 (ACE2) downregulation as a possible pathomechanism of COVID-19-related acute ischemic stroke, which may augment the vasoconstrictor effect of angiotensin II and eliminate the protective role of ACE2 in the cardiovascular and cerebrovascular systems. It is particularly interesting that the surface spike protein on the SARS-CoV-2 virus may bind to ACE2 receptors on platelets, triggering their activation and aggregation, which may play a harmful role in ischemic stroke. Although the incidence of stroke is not particularly high in COVID-19 patients, clinicians should be aware of this possibility.

In addition to its pathological effects, COVID-19 also significantly impacts the healthcare system. The process and outcomes of recanalization therapy for ischemic stroke changed during the COVID-19 era in the Republic of Korea,[5] because of prehospital delays and decreased opportunities for adequate rehabilitation before and after recanalization therapy. This is probably due to patients being more reluctant to visit a hospital, the presence of many safety processes for COVID-19 protection, and the reduced capacity of hospitals due to large numbers of COVID-19 patients. Indeed, the abrupt increase in patient numbers and the inability to accept critical patients in facilities have been serious problems during the pandemic, especially in undeveloped countries.[6]

Neurological manifestations in patients with COVID-19 admitted to the Central Infectious Diseases Hospital are summarized in another article. Neurological symptoms were present in 186 of 331 patients admitted from March 2020 to September 2020.[7] Those authors found that stroke, seizure, and altered consciousness were significantly associated with the severity of COVID-19.

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Healthcare professionals should be aware of unusual neurological manifestations of COVID-19. Acute confusion could be the initial manifestation of SARS-CoV-2 infection, especially in elderly patients. Direct neuroinvasion of the virus and systemic inflammatory processes may play a role in acute confusion.[8] In another review of both large-scale studies and case reports of COVID-19-associated encephalitis and encephalopathy, the authors found that patients with encephalopathy/encephalitis were generally severely or critically ill, with almost all patients having lung abnormalities.[9] Some patients presented with the SARS-CoV-2 virus in their cerebrospinal fluid.[9] ACE2-related cell entry and central nervous system invasion, cytokine storm, coagulopathy, hypoxia, and molecular mimicry have all been suggested as possible culprits.

Guillain-Barré syndrome (GBS) is a relatively uncommon but profound neurological manifestation of COVID-19. A large cohort study found 6 cases of GBS among 10,881 new-onset neurological complications associated with COVID-19.[1] The reported prevalence (approximately 0.06%) was higher than that observed in the general population (typically 0.001% to 0.004%). A case report also described a patient with facial diplegia, which occurred 2 weeks after SARS-CoV-2 infection.[10] GBS has also been reported after COVID-19 vaccination. In a review of 73 cases of GBS associated with COVID-19, the authors found that features were similar to classic postinfectious GBS, and suggested that they share the same immune-mediated pathogenic mechanisms.[11] In contrast, a systemic review of 11 cases of Miller Fisher syndrome (MFS) found that different targets and mechanisms might be associated with MFS when COVID-19 precedes this syndrome, considering the relatively uncommon presence of antiganglioside antibodies in patients.[12]

Lastly, JCN has published two case reports on COVID-19 vaccination-related neurological complications: 1) a rare case of vaccine-induced immune thrombotic thrombocytopenia[13] and 2) a possible case of COVID-19-vaccination-related cerebral venous sinus thrombosis.[14] The authors were only able to find a temporal relationship to explain this phenomenon. Vaccination-related neurological adverse events are tending to increase with the continuous increase of the vaccinated population. The great difficulty of demonstrating a direct causal relationship between vaccination and neurological complications makes it necessary to develop clinically useful biomarkers.

The COVID-19 pandemic has brought about a new era in healthcare. As our knowledge of the pandemic continues to evolve, the ongoing improvements in the methods for identifying neurological manifestations of COVID-19 will help us to develop effective healthcare strategies for dealing with new viruses.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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