

COVID-19 Associated Neurological Manifestations

During the ongoing coronavirus 2019 (related disease (COVID-19) pandemic due to severe acute respiratory system virus 2 (SARS-CoV-2), the understanding about the disease is constantly evolving. It became evident early during the course of the pandemic that extrapulmonary and thrombotic manifestations were common. Neurological involvement due to SARS-CoV-2 occurs due to direct viral invasion, inflammation/demyelination or development of prothrombotic state. It affects both the central nervous system (CNS) and peripheral nervous system (PNS).^[1,2] Initial publications on neurological manifestations of COVID-19 described them in the form of symptoms.^[1,2] With the better understanding of the presentations, newer publications describe syndromes rather than symptoms due to the virus.^[3-5] Following the widespread use of COVID-19 vaccination, the post-vaccinal complications have also been described.^[6] As the pandemic is still progressing with further waves in some countries (such as parts of Europe and Africa) and a smoldering phase in others, such as India, and the implementation of large-scale vaccination program, we expect to continue to see manifestations due to both the virus and the vaccines simultaneously hereafter. It is prudent to describe manifestations related to the virus and the vaccines together. The mechanisms of some of the neurological complications such as the strokes, are common to both, whereas the mechanisms for others, such as demyelination, are different between the infection and the vaccines. Then, there are patients who are suffering SARS-CoV-2 infection even after receiving vaccination. Some of these patients may develop neurological complications and so, in such instances, it is necessary to be able to differentiate between the problems due to virus and complications due to the vaccines.

In this issue, George *et al.*^[5] have described most of the manifestations due to both the etiologies and will serve as a useful reference for the clinicians and the future authors. Certain non-serious manifestations appear during the acute phase of the viral infection, which include anosmia, ageusia and constitutional symptoms such as headache, myalgia and fatigue. CNS manifestations due to virus include encephalopathy, encephalitis, strokes, seizures, central and peripheral demyelinating disorders, movement disorders, peripheral neuropathies and rarely, posterior reversible leukoencephalopathy syndrome (PRES).^[1-5] During the second wave of COVID-19, rhino-orbito-cerebral mucormycosis infection following COVID-19 has been described from India.^[7] Data about neurological manifestations is needed from all parts of world to see if any regional variation exists. A point to note is since the COVID-19 infection is widespread, a neurological manifestation in COVID-19 patient can be incidental, triggered or caused by the virus.^[8]

Encephalopathy can be a consequence of high fever, hypoxia, metabolic derangements, sepsis, inflammation, cytokine

storm, prothrombotic state or seizures.^[1,2] Encephalitis is uncommon with COVID-19 infection. Most of the viruses cause encephalitic illness due to direct invasion or as a post-infectious mechanism. SARS-CoV-2 virus also causes acute necrotizing encephalopathy (ANE) which is proposed to be caused by a third mechanism, that is by release of cytokines.^[9] More research needs to be performed to study the pathogenesis of such syndromes. Role of anti-viral drugs, anti-cytokine monoclonal antibodies such as tocilizumab and steroids need to be assessed in patients with brain involvement through properly structured trials. It is difficult to differentiate between encephalitis and encephalopathy in some patients, especially in the patients who have a normal metabolic lab and no evidence of secondary bacterial or fungal infection. Documenting the virus in cerebrospinal fluid may separate encephalitis from encephalopathy, thus solving this issue about the pathogenesis.

SARS-CoV-2 infection is a pro-thrombotic state and arterial ischemic strokes (AIS) are commonly seen around and after COVID-19. Cerebral venous sinus thrombosis has also been reported. Intracerebral hemorrhages as a complication of SARS-CoV-2 infection are comparatively rare.^[10] Superadded fungal infections were a common complication, more so during the second wave of the epidemic. Mucormycosis is an angio-invasive disease and was another cause for AIS as well as hemorrhagic strokes during this period.^[11] All acute stroke management protocols including recanalization measures need to be implemented, weighing the risks and benefits of these therapies with the health care givers using personal protection devices.^[1] Patients have suffered AIS on anti-platelet agents and/or heparin and so, comparative trials need to be set up evaluate the role of anti-coagulation in COVID-19 related AIS.

Seizures can occur in SARS-CoV-2 infection because of several causes. They could be precipitated just by the fever in a known epileptic, fever due to viral infection or vaccine could trigger seizures in a patient with no past history and so could metabolic impairment and secondary sepsis. Seizures can occur due to strokes, encephalitis, necrotizing encephalopathy, post-viral or post-vaccinal acute disseminated encephalomyelitis (ADEM). So, seizures around the period of COVID-19 or after vaccination would need careful evaluation to pinpoint the cause.

Peripheral neuropathy occurs during the course of the acute SARS-CoV-2 infection, as well as after the COVID-19 symptoms subside. So, it is possible that the ones who present early are due to the direct neurotropic effects of the virus and so, can be called infectious or para-infectious, whereas those that follow after the fever and respiratory symptoms have resolved are the classic “post-infectious”, that is Guillain-Barre Syndrome (GBS).^[12] SARS-CoV-2 infection can also cause

mononeuropathies involving both the cranial and the peripheral nerves. Bell's palsy is a known complication. Involvement of single nerve of the limb (ulnar or peroneal neuropathies) has also been documented after COVID-19.^[13] Though severe myalgia and fatigue are extremely common during acute infection and also as a post-COVID syndrome, neuromuscular junction and primary muscle involvement has not been a common occurrence.^[13]

The neurological manifestations of COVID-19 vaccines are best studied for ChAdOx1nCoV-19s vaccine which is most common vaccine used in India.^[6] The manifestations include GBS, Bell's palsy, ischemic and hemorrhagic strokes and demyelinating events. Efforts should be made to find which sub-group of population is more susceptible to post-vaccinal complications.

The 1918 Spanish flu pandemic was followed by the so called "encephalitis lethargica" and there was sharp rise in the incidence of parkinsonism after this pandemic.^[14] A long duration follow-up of COVID-19 patients needs to be undertaken to study the long-term neurological complications of this dreadful viral infection.

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