Editorial Commentary on the Article "Neurological Disorders Seen During Second Wave of SARS-CoV-2 Pandemic from Two Tertiary Care Centers in Central and Southern Kerala"

Covid-19 pandemic caused by SARS Cov2 virus which originated in Wuhan, China has spread to many countries worldwide. The pathophysiology of the SARS Cov2 virus is probably secondary to three mechanisms[1,2]—coagulopathy, cytokine storm, and autoimmunity. Endothelial dysfunction in central nervous system (CNS) involvement in Covid causes microvasculopathy with string vessel formation (basement membrane lined tubes following the death of endothelial cells).[3] One mechanism includes the cleavage of NEMO (Nuclear factor kB essential modulator) by SARS Cov2 protease.[3] Patients with neurological complications have been found to have high levels of D- dimer, IL-6,[4] and tumor necrosis factor alpha (TNF alpha).[5] Patients also present with elevation of Von Willebrand factor and soluble thrombomodulin, providing clear evidence for Covid-mediated endotheliopathy, and with plasminogen activator inhibitor-1 (PAI-1) elevation suggesting platelet activation.[6] The present study by George *et al*,[7] is a retrospective study and the total number of patients sampled is 1270 with 42 patients having neurological manifestations. Stroke was the most common neurological disorder, present in 21 (50%) patients.[7] The etiology of stroke in Covid is multifactorial. Hypercoagulable state and angiotensin-converting enzyme 2 (ACE2) receptor binding leading to increased angiotensin 2 levels are the most important causes.[8] Previous studies have shown that stroke in Covid-19 is more likely to have large vessel occlusions and have a poorer prognosis.[9] Stroke is frequently multi-territorial rendering the procedure of mechanical thrombectomy more complex with high rates of re-occlusion.[10] Covid status of patients should not alter the decision for thrombolysis or in providing mechanical thrombectomy.[11] Modification of protocols to minimize the exposure risks to doctors and patients should be prioritized. As no patient has received reperfusion therapy in the present study,[7] these parameters could not be assessed. Cerebral venous thrombosis (CVT) is reported frequently among Covid patients.[12] In comparison to non-Covid patients, thrombosis burden is higher with the involvement of multiple dural sinuses leading to higher mortality in Covid-induced CVT.[13] Also, this study has reported D dimer elevation in 12 of these patients.[7] A previous study had found D dimer elevation to correlate with mortality in Covid-19 patients.[14] The presentation in this study by George *et al*,[7] of Covid-induced demyelination included retrobulbar neuritis, transverse myelitis, and cauda equina syndrome. In this study, out of the 4 post-vaccine events, 3 were post-Covishield vaccination and 1 was post-Covaxin.[7] As Covishield is a vector-based vaccine, this might explain the higher incidence of adverse effects noted with Covishield in this study. Similar findings have been described in a previous study by Patone *et al*.[15] Given the above findings, it can be deduced that Covid infection and vaccine induce myriad varieties of demyelination. Earlier studies have shown that in patients with Covid-19 infection, the occurrence of seizures and epilepsy is infrequent.[16] The likely mechanism behind the neuronal hyperexcitability is probably cytokine storm.[17] Among the patients with new-onset seizures reported in the present study, one patient was a known case of pregnancy-induced hypertension with imaging suggestive of atypical posterior reversible encephalopathy syndrome. There have been various case reports of posterior reversible encephalopathy being associated with Covid-19.[18,19] Atypical posterior reversible encephalopathy has been rarely reported. Four patients with mucormycosis have been reported, one of them being rhino-orbito-cerebral mucormycosis.[7] As the patients with mucormycosis have been referred to other hospitals due to the non-availability of amphotericin B, the number of patients reported is likely underrepresented. In India, the prevalence of mucormycosis is around 0.14 per 1000, which is 80 times higher than in other developed countries.[20] Mucormycosis' association with the second wave of Covid-19 infection in India is multifactorial. Delta strain, high doses of steroids, and diabetes mellitus are the three most common risk factors.[21,22] A frequently underrepresented risk factor behind the spike of mucor in the second wave was the use of industrial oxygen.[23] The increasing demand for oxygen with increased production and subsequent refilling of cylinders leads to higher contamination. Case reports have emerged on Covid-induced meningoencephalitis.[24,25] A plethora of brain imaging findings is found in Covid-19 ranging from FLAIR signal abnormalities, cortical diffusion restriction, and leptomeningeal enhancement.[26] Encephalopathy in Covid is multifactorial.[27] The etiology includes hypoxia, metabolic, toxic, sepsis, and cytokine storm.[27] Case reports of Covid encephalopathy patients recovering following administration of tocilizumab have emerged suggesting the role of cytokine storm in its genesis.[28] SARS Cov2 causes varied neuromuscular manifestations—Guillain-Barré syndrome (GBS), myositis, or Critical illness neuropathy/myopathy.[29] Patients with Covid-19 induced myositis reported elevated creatine kinase and the inability to isolate the virus from histopathology analysis of muscle has made researchers believe that the pathology is inflammatory.[30] Three patients had Bell's palsy and three had foot drop in the present study.[7] Surprisingly no GBS cases were reported in this study secondary to Covid.[7] The association of GBS with Covid-19 is well known. In a systematic review, the prevalence of GBS in Covid-19 was found to be 0.15%,[31] with the major subtype being demyelinating. It is further divided into post-infectious and para infectious. There was no

major difference in the clinical presentation among Covid and non-Covid patients with GBS, with the management being similar.[32] Case reports have reported Bell's palsy in Covid patients.[33] A study from Karnataka has reported the prevalence of Bell's palsy among Covid-19 patients to be 0.8%.[34] This is significantly higher than the general population. The limitations of this study include small sample size, overrepresentation of severe cases which required hospitalization, a lack of statistical analysis, and an inability to establish causation.

Lakshmi Narasimhan Ranganathan, Kaushik S, Shrivarthan R[1], Guhan Ramamurthy[2]

Institute of Neurology, Madras Medical College, Chennai, Tamil Nadu, [1]Institute of Neurosciences and Spinal Disorders, MGM Healthcare, Vihaa Multispeciality Hospital, Chennai, Tamil Nadu, [2]Department of Neurology and Neurorehabilitation, BG Hospital, Tiruchendur, Tuticorin, Tamil Nadu, India

Address for correspondence: Dr. Lakshmi Narasimhan Ranganathan, Institute of Neurology, Madras Medical College, Park Town, Chennai - 600 003, Tamil Nadu, India.
E-mail: lakshmineuro@gmail.com

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