



## Pathophysiology and Spectrum of Neuro-COVID

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**Abstract:** Some neurological manifestations may not be specific for COVID-19 and due to other causes but that COVID-19 must be considered as a differential of all acute neurological conditions. The following neuropathological abnormalities were found: acute microscopic thrombotic ischemic infarcts; microscopic haemorrhagic infarcts; petechial haemorrhage; focal perivascular parenchymal T-cell infiltrates; diffuse perivascular parenchymal T-cell infiltrates; leptomeningeal inflammation; interstitial brainstem inflammation with neuronal loss; capillary endothelium expression of ACE2 receptors; microglial nodules; and hypoxic ischemia changes and neuronal loss.

**Keywords:** COVID-19, neurological, SARS-CoV-2, brain, nerves.

## LETTER TO THE EDITOR

We appreciated reading the review article by Maramattom, B. V., & Bhattacharjee, S. (2020) about the pathophysiology of the SARS-CoV-2 infection and about the neurological manifestations of COVID-19 (neuro-COVID) (Maramattom, B. V., & Bhattacharjee, S. 2020). Upon a systematic search including the literature published until June 2020 the authors concluded that some neurological manifestations may not be specific for COVID-19 and due to other causes but that COVID-19 must be considered as a differential of all acute neurological conditions (Maramattom, B. V., & Bhattacharjee, S. 2020). We have the following comments and concerns.

The main limitation of the review is that five months of publication have been passed since the literature search and a number of new data about the neurological compromise are now available. There is meanwhile not only a single neuropathological study of COVID-19 patients available but several (Younger, D. S. 2020; & Keller, E. *et al.*, 2020). In a review of 50 decedents from severe COVID-19 undergoing post-mortem studies the following neuropathological abnormalities were found: acute microscopic thrombotic ischemic infarcts (n=4); microscopic haemorrhagic infarcts (n=2); petechial haemorrhage (n=3); focal perivascular parenchymal T-cell infiltrates (n=3); diffuse perivascular parenchymal T-cell infiltrates (n=2); leptomeningeal inflammation (n=7); interstitial brainstem inflammation with neuronal loss (n=6); capillary endothelium expression of ACE2 receptors (n=1); microglial nodules (n=1); and hypoxic ischemia changes and neuronal loss (n=25) (Younger, D. S. 2020). The author concluded that hypoxia-ischemia is evident in the majority of cases but does not account for all relevant neuropathological features of severe COVID-19, that patients presenting with elevated levels of circulating interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- $\alpha$ , suggest activation of innate and adaptive immunity indicative of a cytokine storm, and that some patients may develop ADEM-like features or histologic evidence of brainstem encephalitis (Younger, D. S. 2020). Autopsy of a single patient reported in a study of 32 patients with severe COVID-19 found microbleeds in the pontine tegmentum, microinfarcts in the basal ganglia, extensive subarachnoid haemorrhage around the rostral surface of the cerebellum with multiple fresh microinfarcts and parenchymal haemorrhages in the adjacent cerebral tissue (Keller, E. *et al.*, 2020). In a post-mortem case series of 43 COVID-19 patients, ischemic stroke was found in 6 cases, astrogliosis in 37 cases, and activation of microglia and infiltration by T-lymphocytes in the brainstem, cerebellum and meninges in 34 cases (Matschke, J. *et al.*, 2020). Interestingly SARS-CoV-2 could be detected in 21 patients (Matschke, J. *et al.*, 2020).

Neurological complications resulting from the immune reaction not considered in the review were multiple sclerosis (MS) (Palao, M. *et al.*, 2020), neuromyelitis (NMO) spectrum disorder (de Ruijter, N. S. *et al.*, 2020), cytokine release syndrome, limbic encephalitis (Zambreanu, L. *et al.*, 2020), cerebral vasculitis (Vaschetto, R. *et al.*, 2020), cerebral vasoconstriction syndrome, microbleeds, psychosis, and dermatomyositis [Finsterer, submitted].

The authors also did not consider that affection of the heart may secondarily cause cerebral disease in COVID-19 patients. There is increasing evidence that one of the cardiac manifestations of the viral infection can be myocarditis (Tiwar, T. *et al.*, 2020). Since myocarditis can be associated with systolic dysfunction, supra-ventricular or ventricular

arrhythmias, tamponade, or endocarditis, it is conceivable that intra-ventricular thrombus formation occurs carrying the risk of cardio-embolism and thus, embolic stroke. Watershed ischemic stroke may result from cardiac low output failure in patients with decreased systolic function. Atrial fibrillation or atrial flutter carry the risk of cardio-embolic stroke as well. It is also conceivable that cerebral hypoxia may not only result from hypo-oxygenation due to pneumonia or acute respiratory distress syndrome (ARDS) but also due to ventricular arrhythmias if patients are not intubated and treated on an intensive care unit (ICU).

Another issue not considered in the review is the neuro- or myotoxicity of drugs applied for the treatment of COVID-19. Neurological side effects of such compounds are frequently misdiagnosed as primary involvement in the disease, why such compounds are not discontinued. Drugs known to be harmful to nerves, endplate, or muscle include chloroquine, which may cause myopathy, ritonavir or lopinavir, which may cause myopathy or rhabdomyolysis, azithromycin, which may cause rhabdomyolysis (risk ratio: 2.94), or tocilizumab, which may cause headache or dizziness and reversible cerebral vasoconstriction syndrome (Gonzalez-Martinez, A. *et al.*, 2019), frequent symptoms of COVID-19. A possible complication of the ICU treatment may be critical ill neuropathy or critical ill myopathy.

Guillain Barre syndrome has meanwhile not only been reported in 12 patients, as mentioned in the review, but in >100 patients as per November 2020. How can the CSF be normal in a patient with GBS, since CSF abnormalities are a hallmark of the disease. Though not always present at onset of GBS, dissociation cyto-albuminique is a key clinical feature of the disease and is present in all patients with progression of the disease.

Overall, there is now overwhelming evidence from clinical and neuropathological studies that the central and peripheral nervous system is primarily or secondarily affected by the viral infection and that the clinical manifestations are more widespread than so far anticipated. Neurological manifestations may be subclinical and only detectable on autopsy or clinically evident. Neurological manifestations may be the initial manifestation of the disease and may more frequently develop in severe than in mild COVID-19 cases. Patients with COVID-19 should undergo thorough neurological investigations as soon as they develop neurological or psychiatric manifestations of the disease.

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