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Neurological Complications of SARS-CoV-2 Infection are Manifold and Require Detection of its Pathophysiology

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LETTER TO THE EDITOR

We read with interest the article by [Ramrakhiani, N. *et al*., 2022] on a retrospective, observational study of the neurological complications in a cohort of 83 COVID-19 patients collected between 28th February 2020 and 31st December 2020 in two tertiary neurology centres in Rajasthan [Ramrakhiani, N. *et al*., 2022]. The most common central nervous system (CNS) complication was stroke (41%), followed by seizures (22%), encephalopathy (21%), headache (15%), and vertigo (4%) [Ramrakhiani, N. *et al*., 2022]. The study is impressive but has several limitations.

The main limitation of the study is its retrospective design, which carries the disadvantage that incomplete data can no longer be supplemented, that necessary supplementary investigations can no longer be performed, that data collection was not standardised, and that the correctness of the recorded data can no longer be controlled [Ramrakhiani, N. *et al*., 2022].

A second limitation of the study is that neurological diagnoses were mixed up with symptoms (myalgia, dizziness, headache, vertigo, seizure, hyposmia, hypogeusia) and laboratory findings (creatine-kinase elevation) [Ramrakhiani, N. *et al*., 2022]. For example, in how many of the enrolled patients was headache due to intracerebral bleeding, subarachnoid bleeding, venous sinus thrombosis (VST), reversible cerebral vasoconstriction syndrome (RCVS), meningitis, encephalitis, migraine, or simply stress? We should know the cause of seizures, dizziness, vertigo, myalgia, hypogeusia, and hyposmia. Was myalgia due to myopathy, rhabdomyolysis or myositis? How did the authors differentiate between dizziness and vertigo?

A third limitation is that the number of CNS and peripheral nervous system (PNS) disorders considered was small, which is why the results may be misleading. The spectrum of CNS and PNS disease related to SARS-CoV-2 infections (SC2I) is much broader [Finsterer, J. *et al*., 2021]. CNS not considered includes RCVS, AHNE, AHLE, ANE, ADEM, PRES, MS, NMO-SD, infectious and immune encephalitis, meningitis, pituitary apoplexy, and tension-type headache.

PNS disorders not considered include Parsonage Turner syndrome, polyneuropathy, myasthenia, myasthenic syndrome, and myositis. Furthermore, critically-ill neuropathy is usually a toxic polyneuropathy only secondary due to SC2I and usually due to ICU management, particularly new medications, hypoxia, infectious disease, or immunological disease. In addition, we should know how autonomic neuropathy was diagnosed. Did the one patient with autonomic neuropathy undergo specific autonomic testing or was diagnosis established upon clinical assessment alone without instrumental investigations? What were the clinical manifestations of autonomic neuropathy? One patient with polyneuropathy had diabetes [Ramrakhiani, N. *et al*., 2022]. Did he have diabetic neuropathy?

A fourth limitation is that the term "encephalopathy" was not defined. We should know if the authors mean neurological deficits with normal cerebral imaging, neuropsychological deficits without focal neurological deficits, epilepsy, or cognitive impairment.

Another limitation is that the maximal latency between positive PCR for SC2 and onset of neurological manifestations was not clearly defined. This latency needs to be mentioned as

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neurological disease >30 days after positive for SC2 may not only be due the SC2I but be also due to other causes. Particularly in patients with stroke and cardiovascular risk factors, stroke could be also due to these risk profile the longer the latency.

We disagree with the definition that post-COVID period starts at >14d after initial PCR positivity. The post-COVID period last from week 5 to week 12 after onset of SC2I.

How many had more than single neurological complication?

In summary, the excellent study has limitations that call the conclusions into question. CNS and PNS complications due to a SC2I are more diverse than usually anticipated. To capture the entire spectrum of neurological complications of a SC2I, prospective, multicentre studies are required.

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Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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