

Causality between COVID-19 and Neurological Disease should not be Based Solely on a Temporal Connection

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Abstract: Neurological disease associated with SARS-CoV-2 should only be diagnosed if it occurs after the infection, the time-window between infection and onset of neurological disease is short, a neurological disease is diagnosed that is usually reported as SARS-CoV-2-related, and a SARS-CoV-2 specific immune response is documented in the nervous system.

Keywords: SARS-CoV-2 infection, PCR, neurological complications, stroke, seizures, Guillain Barre syndrome.

LETTER TO THE EDITOR

We read with interest Chang, *et al.*'s article on a prospective study on the neurological complications in COVID-19 patients recruited from all government and private hospitals in Sri Lanka between May 2021 and April 2022 with access to a neurologist [Chang, T. *et al.*, 2023]. Neurological diseases that occurred one week before the onset of COVID-19 or up to six weeks after the onset of COVID-19 were considered to be related to SARS-CoV-2 [Chang, T. *et al.*, 2023]. The most common neurological complication of SARS-CoV-2 infections were ischemic stroke (31%), encephalopathy (13.6%), Guillain–Barre syndrome (GBS) (9.2%), and encephalitis (7.6%) [Chang, T. *et al.*, 2023]. Poor outcome (no recovery or death) was associated with oxygen requirements during admission [Chang, T. *et al.*, 2023]. The study is impressive, but several points require discussion.

The first point is that no explanation was provided according to which criteria a neurological disease was or was not related to SARS-CoV2 infection. In order to assess whether an individual patient actually had a SARS-CoV-2 related neurological disease, it is important to know the inclusion and exclusion criteria in detail.

A specific time window not necessarily implies causality. In particular, a time window of seven days between the onset of a neurological disease and the onset of clinical manifestations of the SARS-CoV-2 infection is not plausible. According to published data, neurological disease associated with SARS-CoV-2 infection begins after the onset of infection [Kawama, K. *et al.*, 2023], making it unlikely that neurological disease is the first manifestation of a SARS-CoV-2 infection before the infection has broken out. What was the reason for including these patients in the study?

It should also be explained why neurological diseases that occurred up to six weeks after the onset of SARS-CoV-2 infection were related to COVID-19 and not due to another cause. We should know how causes other than SARS-CoV-2 infection have been ruled out as the actual cause of neurological disease. Since almost a third of the included patients had an ischemic stroke, it would have been imperative to report whether these stroke patients had cerebrovascular risk factors other than SARS-CoV-2 infection to explain the occurrence of stroke. Since almost 10% of these patients suffered from GBS, it is imperative to rule out more common triggers of GBS such as infection with campylobacter jejuni, Mycoplasma pneumoniae, or the cytomegaly virus [Finsterer, J, 2022].

In addition to a short time window, a causal association between SARS-CoV-2 infection and neurological disease following SARS-CoV-2 infection could be supported if such an association is frequently reported in the literature, such as stroke, seizures, or GBS [Nagubadi, R. *et al.*, 2024], if experimental or animal data indicate such a causal relationship [Sriramula, S. *et al.*, 2023], or if SARS-CoV-2 particles or a specific immune response in the brain can be documented [Akdeniz, S. *et al.*, 2023].

In summary, the excellent study has limitations that should be addressed before drawing final conclusions. Clarifying the weaknesses would strengthen the conclusions and could improve the study. The association of a neurological disease with a SARS-CoV-2 infection should follow strict inclusion/exclusion criteria. Neurological disease associated with SARS-CoV-2 should only be diagnosed if a neurological disease occurs after the infection, if the time window between the infection and the onset of the neurological disease is short, if a neurological disease is diagnosed that is usually

reported as being associated with SARS-CoV-2 infection, and when a SARS-CoV-2 specific immune response can be documented in the central or peripheral nervous system.

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