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Letter to the Editor

## **Diagnosis of Cerebral Involvement in COVID-19 Requires Comprehensive Neurological Workup**

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We read with interest Advani *et al*'s. article on a single-centre, retrospective, and observational study of cerebral imaging findings in 161 SARS-CoV-2-infected (SC2I) patients with clinical neurological manifestations<sup>[1]</sup>. Of the included patients, 13 had ischemic stroke, one each had subdural hematoma, subdural effusion, and subarachnoid bleeding (SAB), and four had intracerebral haemorrhage<sup>[1]</sup>. Mortality was not associated with abnormal cerebral computed tomography (CCT) and those with neurological disease did not have more severe SC2I than those without neurological impairment<sup>[1]</sup>. It was concluded that COVID-19 patients may present with a wide range of CCT abnormalities and that these CCT abnormalities are not associated with mortality or severity of SC2I<sup>[1]</sup>. The study is impressive, but some points require discussion.

A major limitation of the study is its retrospective design. A retrospective design does not allow control of the accuracy of the data stored, does not systematically apply the same examinations to all included patients, produces missing data, does not allow for the addition of missing data, and is not suitable for generating desirable new data.

A second limitation of the study is that only CCT imaging was performed and no contrast agent was used. Disadvantages of CCT are that the resolution is lower compared to MRI and that differentiation between structures is more accurate on MRI compared to CCT. Venous sinus thrombosis (VST) usually cannot be detected on CCT unless a contrast-enhanced CT venography is performed.

A third limitation is that only cerebrovascular diseases were considered as SC2I complications<sup>[1]</sup>. However, the spectrum of cerebral disease complicating SC2I is much broader and also includes infectious meningitis / encephalitis, ventriculitis, immune encephalitis (limbic encephalitis, brainstem encephalitis, cerebellitis), acute disseminated encephalomyelitis (ADEM), acute hemorrhagic encephalitis (AHNE), acute, necrotizing encephalopathy (ANE), multiple sclerosis, neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte glycoprotein (MOG)-associated disease, hypophysitis, cerebral vasculitis, pontine myelinolysis, posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS), opsoclonus-myoclonus syndrome, Wernicke encephalopathy, psychosis, and delirium<sup>[2]</sup>.

A fourth limitation of the study is that it does not report how many subjects had normal CCT but neurological abnormalities on clinical examination. CCT may be non-informative, particularly in patients with meningitis, encephalitis, or VST. It is also not reported how many of the included patients underwent lumbar puncture and cerebrospinal fluid (CSF) studies.

For patients with ischemic stroke, we should know how many patients had classic cardiovascular risk factors. We should also know how the authors distinguished between ischemic stroke due to SC2I and ischemic stroke due to pre-existing cardiovascular risk factors, Have alternative causes of ischemic stroke been thoroughly ruled out before attributing ischemic stroke to SC2I?

Regarding the individual patient with SAB, we should know whether SAB was aneurysmal or non-aneurysmal. Was resection or coiling necessary in the event of an aneurysm?

We do not agree with statement in the introduction that COVID-19 is a multisystem disease<sup>[1]</sup>. In most cases, COVID-19 is restricted to the lungs and therefore a mono-system disease. However, multisystem involvement can occur.

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. The spectrum of cerebral imaging abnormalities in SC2I patients is more widespread than reported in the index review.

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**Statement of Ethics:** a) The study was approved by the institutional review board. b) Written informed consent was obtained

from the patient for publication of the details of their medical case and any accompanying images.

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