Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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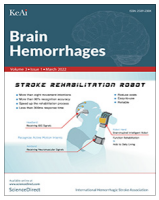

Establishing causality between SARS-CoV-2 and stroke/bleeding requires a temporal relationship and plausible pathophysiology

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ABSTRACT

Cerebrovascular events are increasingly recognized as a complication of SARS-CoV-2 infections. They can be due to hypercoagulability, vasculopathy, cardiac involvement in the infection, or autonomic dysfunction. However, establishing a causal relationship between cerebrovascular events and viral infection is not always easy and requires thorough investigation and documentation of a close temporal relationship between SARS-CoV-2 infection and the onset of cerebral impairment. Establishing a causal relationship between SARS-CoV-2 infection and cerebrovascular events is desirable as it can guide therapeutic management and determine the outcome.

Letter to the Editor.

We read with interest the article by Deana et al. about five patients with cerebrovascular complications of SARS-CoV-2 infection [1]. Patient-1 was diagnosed with venous sinus thrombosis (VST), patient-2 with basilar artery occlusion, patient-3 with left middle cerebral artery ischemic stroke, patient-4 with intracerebral hemorrhage, and patient-5 with subarachnoid bleeding from an aneurysm of the ophthalmic artery [1]. Only patient-1 and patient-3 survived, while the other three patients died, patient-3 and patient-4 from brain death and patient-5 from respiratory failure [1]. The study is promising but raises concerns that should be discussed.

The main limitation of the study is that a causal relationship between SARS-CoV-2 infection and neurological impairment is not supported, at least in three patients. The latency between the positive SARS-CoV-2 PCR test and the basilar artery thrombosis in patient-2 was 45 days, making a causal relation rather unlikely.

Also in patient-2 the latency between the positive PCR test and VST was quite long (42 days), suggesting that there was a fortuitous rather than a causal relationship between the two events. Another argument against a casual relationship is that patient-2 had arterial hypertension, suggesting that the basilar artery thrombosis may be due to atherosclerosis or hypertensive crisis rather than endothelial damage or hypercoagulability from SARS-CoV-2 infection.

There is no convincing evidence that the subarachnoid bleeding (SAB) in patient-5 was related to SARS-CoV-2 infection. The patient had an aneurysm of the right ophthalmic artery, the rupture of which was blamed for the SAB [1]. However, there are several causes other than COVID-19 that could explain rupture of the aneurysm. It may have been a spontaneous rupture, a rupture due to arterial hypertension, or a rupture due to trauma, or embolization.

Another limitation of the study is that none of the five patients underwent multimodal MRI and that no MR venography was performed. In order to assess the extent and acuteness of ischemic stroke, and design a treatment concept, it is crucial to perform multimodal MRI, including T1, T2, FLAIR, DWI, ADC, PWI, and SWI sequences. Multimodal MRI will allow to more accurately assess the prognosis of stroke than cerebral CT (CCT) [2].

There is a discrepancy between the description of patient-5 detailing that the patient had no lung involvement in COVID-19 and the statement that the patient died of respiratory failure due to SARS-CoV-2 infection [1]. This discrepancy should be resolved.

Abbreviations: ADC, apparent difusion cefficient; CCT, cerebral computed tomogrpahy; DWI, diffusion wieghted imaging; ECMO, extra-corporal membrane oxigenation; FLAIR, fluid attenuated inversion recovery; ICB, intracerebral bleeding; PE, pulmonary embolism; PWI, perfusion wieghted imaging; SWI, susceptibility weighted imaging; VST, venous sinus thrombosis.

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Regarding patient-4, we should be informed why surgical treatment was not feasible [1]. Was this due to the thrombopenia or renal failure? What was the cause of renal failure and thrombopenia? Risk factors for ICB in COVID-19 patients are therapeutic anticoagulation, ECMO, and mechanical ventilation [3]. Did the patient require anticoagulation or ECMO in addition to ventilation?

Patietn-3 had severe COVID-19 but nevertheless pulmonary embolism (PE) was diagnosed upon chest CT [1]. Pulmonary embolism is usually diagnosed by spiral perfusion CT of the pulmonary arteries. We should know whether PE was diagnosed by unenhanced CT of the lungs or by perfusion CT.

Patient-2 underwent an "angiographic endovascular procedure". We should know if this means thrombectomy or intraarterial thrombolysis, or did the patient receive systemic thrombolysis?

It lacks the current medications the five patients received for COVID-19 during hospitalisation and the drugs they were taking during hospitalisation and prior to admission for comorbidities.

A further limitation of the study is that reference limits for laboratory tests given in table 1 were not reported. It is therefore, not possible to judge which of the values given were increased, decreased, or normal.

Overall, the interesting study has limitations that call the results and their interpretation into question. Addressing these limitations could further strengthen and reinforce the statement of the study. Establishing a causal relationship between SARS-CoV-2 infection and cerebrovascular events requires a temporal link and a plausible pathophysiological explanation.

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