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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Letter to the Editor

Hemorrhagic stroke in hispanics with severe SARS-CoV2 infection

Clinical/Scientific Note

An increasing body of evidence suggests that the coronavirus disease 2019 (SARS-CoV2) may be associated with cerebrovascular disease, although most cases have been ischemic strokes related to occlusion of major intracranial vessels [1–3]. Intracranial hemorrhages in the setting of SARS-CoV2 infection are exceedingly rare. To the best of our knowledge, only two cases has been reported in detail, one with a massive parenchymal brain hemorrhage and the other with an aneurysmal subarachnoid hemorrhage [4,5]. One additional patient was just mentioned (no details) in a large series of patients with neurological complications related to this infection [3], and the last reported patient had a secondary hemorrhagic transformation of a cerebral infarction after thrombectomy [5]. Here, we report our experience with two patients with SARS-CoV2 who developed an otherwise unexplained intracranial hemorrhage. These cases represented the 1.5% of 132 consecutive patients with SARS-CoV2 admitted to Clínica Guayaquil (Guayaquil, Ecuador) over a two-month period. Four additional patients of the above-mentioned series had ischemic strokes (likely related to large vessel disease in three and to cerebral hypoperfusion in one), but were not the subject of this report.

The two patients with SARS-CoV2 infection who developed an otherwise unexplained intracranial hemorrhage were women, aged 78 (case 1) and 65 (case 2) years, respectively. Diagnosis had been confirmed by detection of coronavirus 2 (CoV-2) viral nuclei acid in nasopharyngeal swab specimens by the use of Real-Time Reverse-Transcriptase-Polymerase Chain Reaction assay. Both were admitted to the Intensive Care Unit (ICU) because of severe acute respiratory syndrome (SARS) requiring artificial mechanical ventilation. At the time of admission to the ICU, the two patients had a normal neurological examination. With the exception of one patient (case 2) with controlled arterial hypertension, there were no risk factors for ICH such as hypertension, alcohol use, cigarette smoking, or use of any oral anticoagulants and/or antiplatelet agents. During their hospital stay, blood pressure remained below 140/90 mmHg. There was no evidence of abnormal heart rhythms on ECG monitoring. Decreased level of consciousness, off sedation, prompted CT. Unenhanced CT showed parenchymal brain hemorrhages in both of them. Further neuroimaging investigation was not possible because of the poor clinical status of the patients. Although, venous thrombosis could not be entirely excluded, there was no evidence of hyperdense veins, dural sinus or sinus distention to suggest acute venous thrombosis in any of the ICH cases. Hemorrhages were located in the head of the right caudate nucleus in Case 1, and in the left temporal lobe in Case 2; both hemorrhages showed extension into the ventricular system (Fig. 1). Blood cells counts, coagulation parameters, glomerular filtration rate, and liver function tests were within normal limits before and after the bleeding episodes. In contrast, D-dimer, C reactive protein and ferritin levels were elevated in both cases. With the exception of subcutaneous enoxaparin (40 mg/day), the patients had not been receiving medications known to increase the risk of bleeding. Patients died 24 and 48 h after the CT scan, respectively. Autopsies were not performed.

Several other viral infections, including dengue virus, West Nile virus, herpes simplex, and VZV infections, have been associated with ICH. The mechanism appears to be multifactorial with vasculitis, coagulopathy, and platelet dysfunction. Pathogenic mechanisms involved in SARS-CoV2 – associated hemorrhagic stroke have not been elucidated [8]. It is plausible to assume that the affinity of the virus (SARS-CoV-2) for ACE2 receptors (expressed in endothelial and arterial smooth muscle cells in the brain) allows the virus to damage intracranial arteries, causing vessel wall rupture and hemorrhages [6]. It is also possible that the “cytokine storm” that accompanies this disorder could promote hemorrhagic stroke, as suggested in a SARS-CoV2 patient who developed an acute necrotizing encephalopathy associated with late parenchymal brain hemorrhages [7].

While the two patients reported here developed otherwise unexplained intracranial hemorrhages, we cannot completely rule out the presence of competing etiologies since CT angiography, a brain MRI, or MRA of intracranial vessels were not performed due to the poor status of the patients. Hemorrhages in cerebral lobes and in the head of the caudate nucleus are often related to arterial hypertension, but may also be caused by the rupture of a cavernous angioma, a small arteriovenous malformation or an intracranial aneurysm, which cannot be detected with an unenhanced CT only. However, both hemorrhages occurred in the setting of severe (and late) SARS-CoV2 disease, in the absence of a sudden increase in blood pressure or other risk factors that may explain

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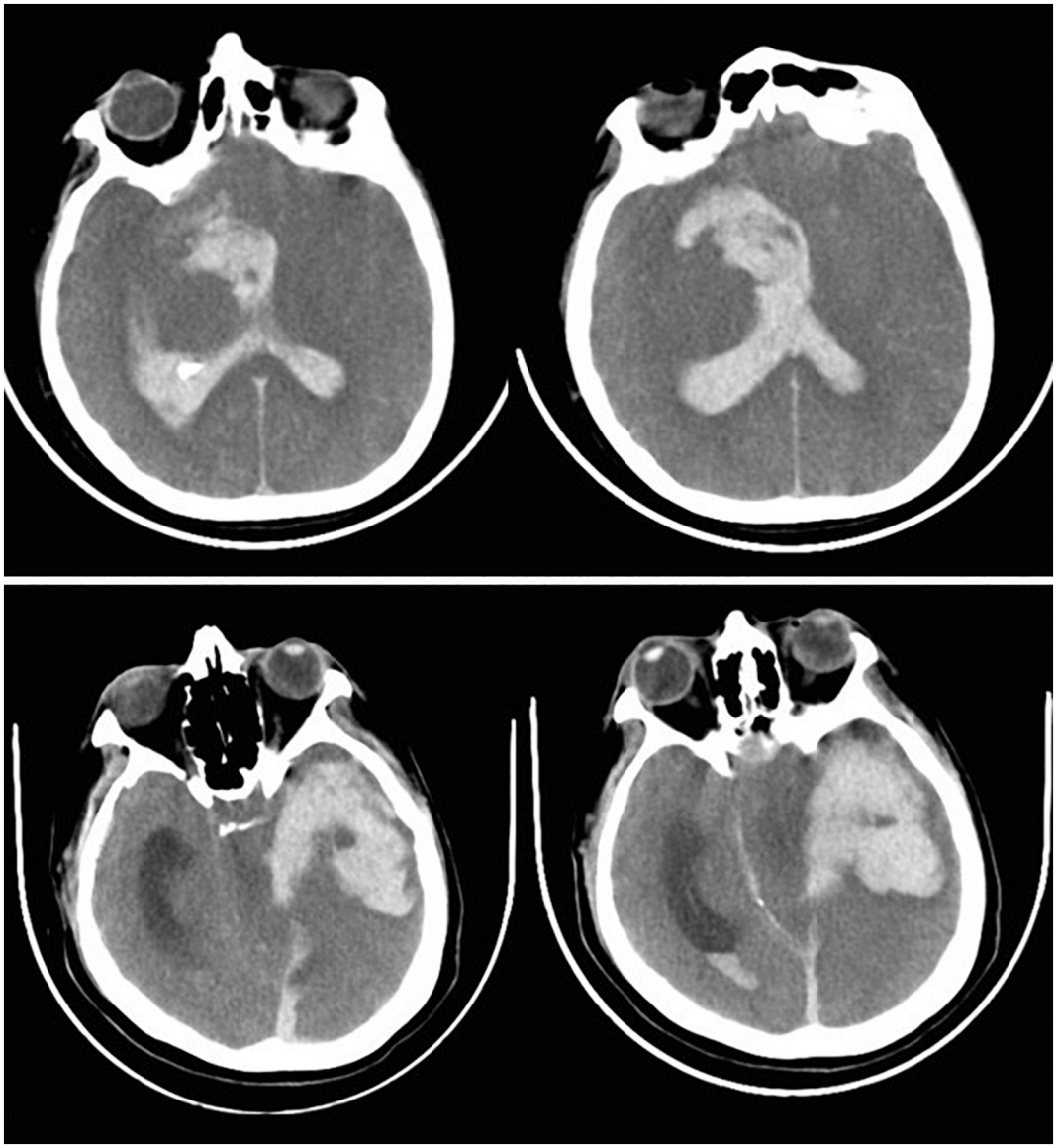

Fig. 1. CT of two patients with COVID-19 infection and hemorrhagic strokes. Upper panel shows a hemorrhage in the head of the caudate nucleus with extension into the ventricular system, and lower panel shows a huge lobar hemorrhage in the left temporal lobe, also with extension into the ventricular system.

the bleeding. Further studies are needed to get more insights on the causal relationship between SARS-CoV2 infections and hemorrhagic strokes.

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Declaration of Competing Interest

The authors declare no conflicts of interest to disclose.

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