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LETTER TO THE EDITOR

Deep cerebral venous sinus thrombosis with transient antiphospholipid antibodies in COVID-19 disease

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Dear Editor,

In March 2020, the World Health Organization, declared coronavirus disease 19 (COVID-19), caused by an infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic. Although it is mainly a severe acute respiratory syndrome with systemic inflammation and coagulopathy, reports of neurological manifestations of SARS-CoV-2, including deep cerebral venous sinus thrombosis (CVST), are emerging [1, 2]. We report a case of CVST without respiratory distress as a presenting symptom of COVID-19 infection accompanied by transient antiphospholipid antibodies.

Case presentation

A 44-old woman, with a medical history of migraine, primary familial hemochromatosis and inflammatory bowel disease, presented at the emergency department in March 2020 with decreased consciousness (GCS of 10), left spastic hemiparesis, and bilateral Babinski signs. She reported a 3-day history of continuous headache with gradual onset and increasing severity. At presentation, she had no respiratory symptoms, and a low-grade fever (38 °C). Blood investigation showed elevated D-dimer values of 1.9 µg/ml (normal values < 0.48 µg/ml), a slightly increased CRP of 19.0 mg/dl (normal value < 3.0 mg/dl) with normal white cell blood count. Non-contrasted brain CT showed multiple hypodensities with hyperdense areas, involving the right thalamus, left caudate nucleus, and left globus pallidus. One day after admission, she was intubated due to further neurological deterioration and transferred to the intensive care unit of our hospital. Contrast chest CT showed no pulmonary embolism, nor lung parenchyma abnormalities consistent with pneumonia or acute respiratory distress syndrome. Brain MRI imaging showed progressive vasogenic oedema in the basal ganglia and deep white matter, with the presence of a deep cerebral vein thrombosis within the internal cerebral veins, inferior sagittal sinus, straight rectal vein, and vein of Rosenthal (Fig. 1). Screening tests for thrombophilia were negative, as well as all autoimmune tests (including antinuclear and antidouble-stranded DNA antibodies, lupus anticoagulant, and anti-beta 2-glycoprotein), apart from anticardiolipin immunoglobulin G antibodies (a marked elevated titer of 45 GPL U/ml). She was screened for COVID-19 as a possible risk factor for her prothrombotic state. The nasopharyngeal swab for SARS-CoV-2 was positive. The patient needed prolonged mechanical ventilation but was weaned through a tracheostomy, and a therapeutic regimen with low molecular weight heparin was given (initiated after diagnosis on brain MRI). A brain MRI, one month after admission, showed partial recanalization of the deep venous cerebral thrombosis with decreased cerebral vasogenic oedema. Her neurological condition further improved and, at day 45, she was transferred to the primary referring hospital for further rehabilitation. Six months later, she had minimal spastic hemiparesis, dysphagia and multiple cognitive deficits. There were no antiphospholipid antibodies detectable six months after presentation.

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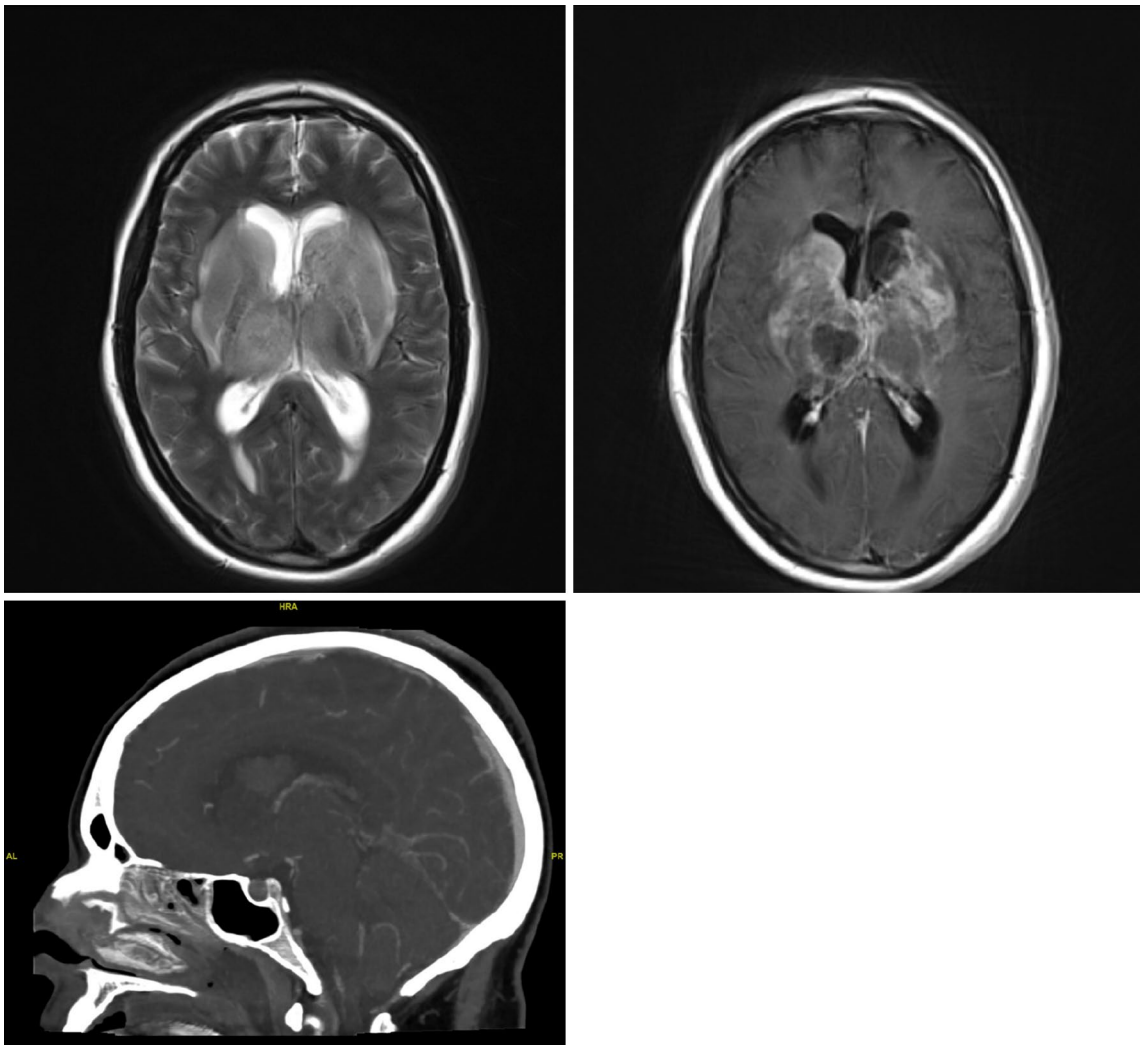

Fig. 1 Brain imaging at presentation. **1** Axial brain MRI, T2-weighted image. Bilateral hyperintensities in basal ganglia and deep white matter. **2** Axial brain MRI, T1-weighted image with Gadolinium. Bilateral contrast enhancement in basal ganglia and deep white matter, with hypo-intensities in left caudate nucleus and right thalamus, compatible with an acute hemorrhage. **3** Sagittal brain CT venogram. Deep cerebral vein thrombosis within the internal cerebral veins, inferior sagittal sinus and straight rectal vein

Discussion

Cerebral venous thrombosis accounts for 0.5–1% of strokes, and often remains a diagnostic challenge as the clinical presentation of CVST is highly variable. However, CVST should be considered in young patients with unusual headache or with stroke-like symptoms in the absence of typical cardiovascular risk factors, and in patients with CT evidence of (multiple) haemorrhagic infarcts, especially when not confined to the arterial vascular territories [3], such as in our patient. There are several inherited and acquired risk factors for CVST. Although inflammatory bowel disease (not active at the time of presentation) is a known risk factor of CVST [3], the presence of COVID-19 is certainly an additional risk factor [2]. It is increasingly recognized that a SARS-CoV-2 infection is associated with a prothrombotic state, with higher numbers of venous and arterial thrombotic events, despite prophylactic and even curative anticoagulation [2, 4]. First, there is emerging evidence that concomitant haemostatic abnormalities, including disseminated intravascular coagulation, occur in COVID-19 patients [4]. Second, severe inflammatory responses and direct effects of SARS-CoV-2 infection, such as severe illness and hypoxemia, may also predispose patients to these prothrombotic events [4]. Moreover, our patient also had positive anticardiolipin antibodies at presentation. There is growing evidence that antiphospholipid antibodies (including anticardiolipin antibodies) are an important cause of secondary hypercoagulable state and

play a role in venous and arterial cerebral infarcts [2, 3]. Transient antiphospholipid antibodies can be triggered by acute viral infections, including cytomegalovirus, varicella zoster and parvovirus B. It seems that SARS-CoV-2 also can trigger such antiphospholipid antibodies, as they have been reported in critically ill COVID-19 patients i.e. with multifocal strokes [5]. However, the clinical significance of finding these virus-induced antiphospholipid antibodies remains unknown. In some patients, including our patient, they disappear within 3 months after the viral infection, meanwhile in others they persist and raise the question of whether these viral infections may trigger pathogenic antiphospholipid antibodies in underlying autoimmune diseases [5]. Further research to confirm this hypothesis is warranted.

Cerebral venous thrombosis has been described as a thrombotic complication of coronavirus-19 respiratory disease [2, 4], however our patient did never experience an acute respiratory syndrome prior to this presentation. Therefore, clinicians should carefully consider CSVT, without respiratory signs or typical CT-hallmarks of COVID-19 related pulmonary damage, as an unusual presenting symptom of COVID-19, especially when additional prothrombotic risk factors, such as systemic inflammatory diseases or (transient) antiphospholipid antibodies, are present.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest to disclose.

Ethical approval No supplementary interventions have been performed other than the indicated diagnostic interventions. All diagnostic investigations performed in this case report and involving the single human participant have been in accordance with the Declaration of Helsinki of 1964. This article does not contain any studies with animals performed by any of the authors.

Consent for publication Informed consent for publication was obtained.

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