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.

Journal of Neuroradiology 48 (2021) 65–67

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COVID-19 as triggering co-factor for cortical cerebral venous thrombosis?

We report a clinical case of an isolated cortical cerebral venous thrombosis (CVT), without any history of genetic or acquired thrombophilia, associated with COVID-19. Up to now, a few cases of sinus CVT have been reported to be possibly linked to a SARS-CoV-2 infection [1–5]. This is however, to our knowledge, the first description of a case with an associated cortical CVT. Other brain imaging abnormalities (arterial stroke or images compatible with acute disseminated encephalomyelitis) have been described [6]. The COVID-19 is caused by the SARS-CoV-2. This coronavirus activates inflammatory and thrombotic pathways by binding the angiotensin-converting enzyme 2 receptors of endothelial cells, leading to an endotheliitis and a diffuse procoagulant state [7]. Our case suggests that the cerebral venous system can also be affected by this pathologic process.

A 33-year-old female patient, with a combined estrogen-progestin oral contraception (ethinylestradiol 0.02 mg/day and gestodene 0.075 mg/day; monophasic 21-day pills), developed an unusual, bilateral and moderate headache on March 22nd, 2020. The following day, she had a fever (39 °C), diffuse myalgia, and cough with increased headache intensity. One week later, the clinical picture was completed by a slight dyspnea, anosmia and dysgueusia. All symptoms and signs disappeared three weeks later, except for the headache, which persisted and progressively worsened. On April 27th, 2020, she suffered from a partial complex epileptic seizure with secondary generalised convulsions, treated with levetiracetam (1 g/day). On admission, general and neurological clinical examination was unremarkable. However, we noted that she had a body mass index (BMI) of 34.6 kg/m^2 (normal range 20–25). Usual blood tests were normal, except for a very slight increase of fibrinogen at 4.2 g/L (normal range 2.0–4.0) and a more significant elevation of the D-Dimers (902 ng/mL, normal < 500). Other routine coagulation tests were normal. The chest-CT scanner was rated as “no CT findings present to indicate pneumonia” (Cov-19Neg) according to Radiological Society of North America consensus statement classification [8]. The SARS-CoV-2 Polymerase Chain Reaction (PCR) nasopharyngeal testing was positive. The brain Magnetic Resonance Imaging (MRI) examination demonstrated a left parietal cortical CVT with neither parenchymal infarction (negative diffusion-weighted imaging) nor hemorrhage but with adjacent vasogenic edema due to focal upstream venous overpressure (Fig. 1). Oral anticoagulation treatment with dabigatran 150 mg, b.i.d. was initiated. Combined estrogen-progestin oral contraception was interrupted. Complete relief of headaches was obtained five days after anticoagulation initiation. Further analyses of hemostasis were normal, including g20210a factor II mutation, antithrombine III, protein C, protein S and activated protein C resistance. Serum antiphospholipid, antinuclear and anti-neutrophils cytoplasm antibodies were not detected. Serum SARS-CoV-2 antibodies were positive at 110,6UA/mL (Elecsys® Anti-SARS-CoV-2, Roche), eight weeks after the first symptoms.

COVID-19 infection is a systemic disease caused by SARS-CoV-2. Several observational studies have shown a high proportion of thromboembolic events in patients infected by the agent [9–11]. Varga et al. established evidences for direct viral infection of the endothelial cells with local accumulation of inflammatory cells [7]. The authors suggested that the SARS-CoV-2 could facilitate the development of endotheliitis in several organs resulting in a global procoagulant state [7].

A thorough review of the available literature (till June 8th, 2020) found five observational reports suggesting an association between COVID-19 and CVT [1–5]. Only one of them gave data on research of potential thrombophilic state [4].

CVT is an uncommon cause of stroke. The incidence has been evaluated to 15.7 per million inhabitants per year [12]. Many medical conditions have been identified as risk factor of CVT, such as acquired or genetic thrombophilia, and either specific local causes including head, face or neck infections or some systemic diseases [13]. Cortical CVT is reputed to be more likely to induce seizures [14].

Our patient had two risk factors for developing a CVT: a high BMI and the use of a combined estrogen-progestin oral contraception. We did not find any genetic or acquired thrombophilia condition associated with CVT. No other conditions inducing hypercoagulability were detected, except for the COVID-19. Therefore, we hypothesise that COVID-19 has played a synergistic role as risk factor for the patient’s cortical CVT. It needs to be highlighted that our patient suffered from a headache from the earliest onset of the disease course, without recovery, until the oral anticoagulation was initiated, almost 6 weeks after the onset of the headache. Importantly, all other usual COVID-19 symptoms (fever, myalgia, cough, dyspnea and anosmia) subsided within 21 days of their appearance.

Although a causal relationship between the SARS-CoV-2 infection and the development of the cortical CVT of our patient cannot be definitely demonstrated, we suggest COVID-19 to be a risk factor based on the temporal relationship, the absence of another cause of hypercoagulability, and plausible pathophysiological mechanisms.

https://doi.org/10.1016/j.neurad.2020.06.008
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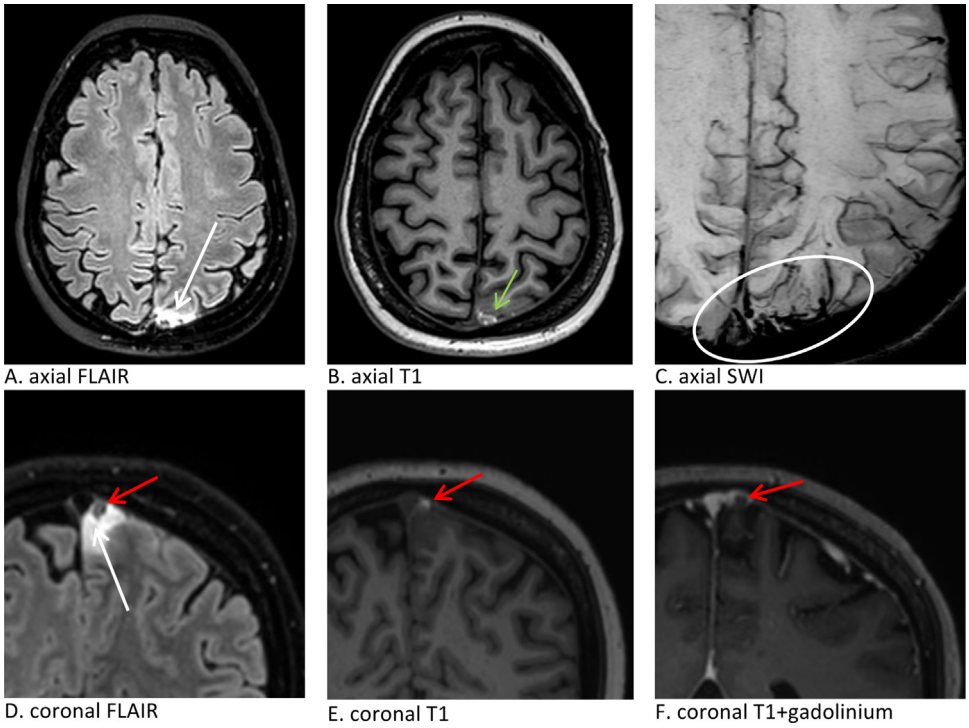

Fig. 1. Images A and D demonstrate parenchymal hyperintensity on FLAIR/T2-weighted views (white arrows), revealing a vasogenic edema in the cortex of the left superior parietal lobule. Diffusion-weighted imaging (DWI) was negative excluding a cytotoxic edema (not shown). Cortical CVT is indicated with red arrows in FLAIR view on D (hyposignal due to deoxyhemoglobin), in pre-contrast T1 weighted view on E (hypersignal due to methemoglobin) and in post-contrast T1-weighted view on F (hyposignal due to the signal intensity switch featuring the so-called "delta sign"). Image B shows 3 hyperintense spots featuring the methemoglobin-containing subacute endoluminal clot (green arrow). Susceptibility-weighted imaging (SWI, image C) reveals the dilatation of the surrounding upstream venous network (white circle).

Ethics approval

This case-report received the approbation of the President of the local ethics committee.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Authors' contributions

CB and MPR searched the literature and drafted the manuscript. MPR designed the figure with input of TD. All authors commented on and revised the final manuscript.

Disclosure of interest

MPR has received funding from Boehringer-Ingelheim for clinical trials and advisory board fees. The other authors declare that they have no competing interest.

Acknowledgements

We wish to thank the patient for her consent for the publication, Professor Niloufar Sadeghi (Imaging Department, ULB Erasme Hospital, Brussels) for her important contribution to the diagnosis and Dr Sarah Debray, Dr Michel Gille, Dr Perrine Paindeville, Dr Françoise Piéret and Mrs Serena Merve Myriam Cigdem for their contribution to the article.

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Available online 27 June 2020