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LETTER TO THE EDITORS

Cytotoxic lesions of the corpus callosum (CLOCCs) associated with SARS-CoV-2 infection

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Dear Sirs,

Although coronavirus disease-2019 (COVID-19) mostly affects the respiratory system [1], neurological manifestations have already been described in COVID-19 patients [2]. Here, we report a case of neurological symptoms associated with cytotoxic lesions of the corpus callosum (CLOCCs) in a COVID-19 patient.

A 26-year-old patient, without any medical history, was admitted for dry cough and acute confusion for 2 days. He was awake but agitated and disoriented, exhibiting violent behavior and inappropriate speech. On clinical examination, no focal or meningeal signs were reported. Body temperature was 40 °C and oxygen saturation on room air was 100%. Laboratory tests results included increased C-reactive protein level [200 mg/l; normal value (NV): < 5 mg/l], lymphopenia (1090/µl; NV: 1200–3500/µl), thrombocytopenia (95×10^3/µl; NV: 150–440×10^3/µl), elevated D-dimers (4466 ng/ml; NV: < 500 ng/ml), ferritin (1278 µg/l; NV: 30–300 µg/l), high-sensitivity troponin I (226 ng/l; NV < 14 ng/l) and IL-6 (132 pg/ml; NV ≤ 1.8 pg/ml) levels. Cerebro-spinal fluid was crystal clear, with 3/µl white blood cell and normal protein levels. Polymerase chain reaction (PCR) on CSF for neurotropic viruses was negative. Search for autoantibodies and serological tests for human immunodeficiency virus and syphilis tested negative. Three reverse real-time PCR (rRT-PCR) assays for SARS-CoV-2 on nasopharyngeal swabs were negative. Trans-thoracic echocardiography revealed biventricular dysfunction with diffuse hypokinesia and left ventricular ejection fraction of 35%, suggestive of myocarditis. Thin-section chest computed tomography showed bilateral crazy-paving patterns, suggestive of COVID-19. Brain magnetic resonance imaging (MRI; Fig. 1) on admission revealed a round lesion in the splenium of the corpus callosum, hyperintense on fluid attenuated inversion recovery (FLAIR) and T2-weighted imaging with restricted diffusion, compatible with the diagnosis of cytotoxic lesions of the corpus callosum (CLOCCs). An electroencephalogram showed mild encephalopathy with no epileptiform discharges. Serological blood test for SARS-CoV-2 IgG (DiaSorin-Saluggia, Italy) tested positive (34 AU/ml; cutoff = 12 AU/ml). The treatment was conservative. The neurological status of the patient improved in the next 48 h and his cardiac dysfunction resolved within a week. Control MRI performed three weeks later was normal (Fig. 1).

CLOCCs are non-specific findings on brain MRI associated with reversible neurological signs, such as behavior changes and multiple etiologies, including viral illness, drug toxicity, seizures, malignancy, subarachnoid hemorrhage and metabolic disturbances [3]. The physiopathological hypothesis is that an inflammatory process involving cytokines such as IL-6 triggers the accumulation of glutamate in the extracellular space, resulting in cytotoxic edema, in particular of astrocytes. The selective vulnerability of the corpus callosum could be explained by its high density of cytokine and glutamate receptors [3]. CLOCCs has been reported in several viral infections [3], but this is the first description

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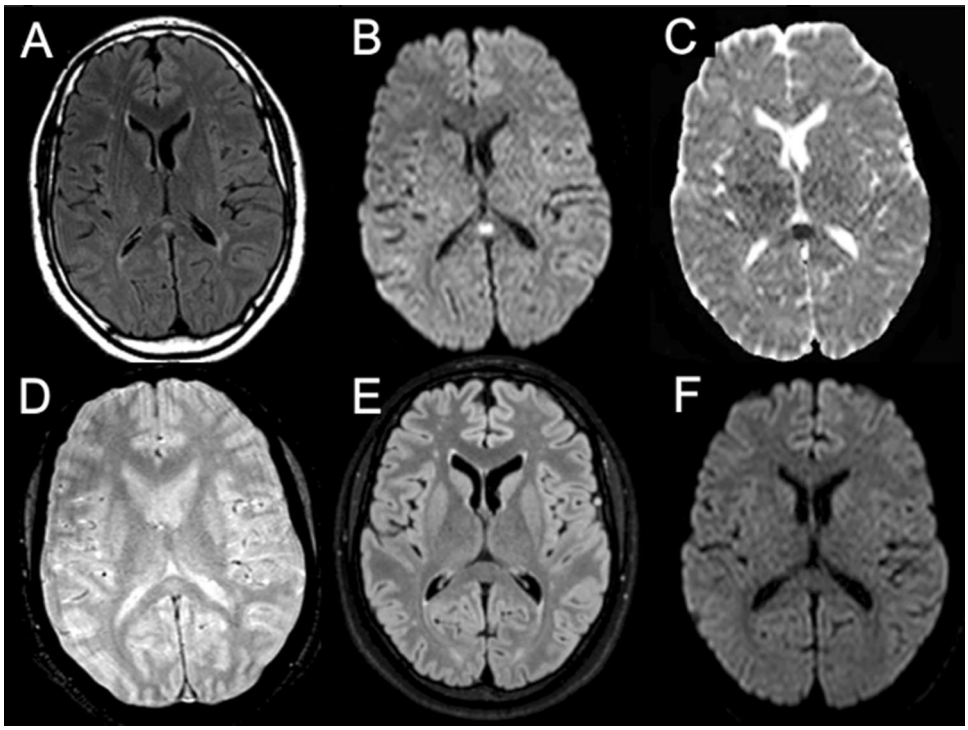

Fig. 1 Brain magnetic resonance imaging (MRI), performed the day after admission, revealed the presence of a well-circumscribed oval lesion within the splenium of the corpus callosum. The lesion demonstrates the features of cytotoxic edema: hyperintensity in fluid-attenuation inversion recovery (FLAIR) sequence (**a**) and restricted diffusion displayed by an area of high signal intensity on diffusion-weighted imaging (DWI; **b**) and low signal intensity on apparent diffusion coefficient (ADC; **c**) map. There is no hemorrhage on gradient echo T2-weighted imaging (**d**). Control MRI showed complete resolution of the lesion on FLAIR (**e**) and DWI (**f**) sequences

of association with SARS-CoV-2 infection. Clinical and laboratory findings were not suggestive of any of the other above-mentioned conditions. Despite two negative rRT-PCR assays, chest-CT findings, high IL-6 level [4] and a positive serological test confirmed the diagnosis of COVID-19, which had likely occurred at least 2 weeks before admission [5]. This case further expands the spectrum of acute neurological complications of COVID-19. Mao et al. [2] reported that 36% of COVID-19 patients had neurological manifestations, including encephalopathy, acute cerebrovascular diseases and skeletal muscle injury. Interestingly, complications such as Guillain–Barré syndrome, Miller–Fisher syndrome or demyelinating lesions of the central nervous system [6–8] have also been reported, suggesting immune-mediated post-infectious mechanisms associated with SARS-CoV-2. Other mechanisms of neurological disorders are direct invasion of the brain via the olfactory bulb, carriage across the blood–brain barrier following viremia or entry through infected leucocytes [9].

In conclusion, we reported the first case of CLOCCs associated with SARS-CoV-2 infection. Serological blood tests could be helpful for the diagnosis of SARS-CoV-2-associated complications.

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Compliance with ethical standards

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