Neurological Sciences (2022) 43:4103–4105
https://doi.org/10.1007/s10072-022-06040-9

COVID-19

Posterior reversible encephalopathy syndrome: an atypical neurological manifestation of SARS-CoV-2 infection

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Received: 19 March 2022 / Accepted: 21 March 2022 / Published online: 1 April 2022

Dear Editor in Chief,

The coronavirus disease-19 (COVID-19) pandemic is still ongoing with serious implications affecting daily lives and social gatherings, posing a significant mental health burden on society. The characterization of neuropsychological manifestations in COVID-19 is complex as it encompasses psychosocial factors, virus-related injury mechanisms, and neurological immune-mediated damage.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has shown intrinsic neurotropism and may cause direct damage to the central nervous system (CNS) during acute infection and post-infective neurological complications. The virus binds to the angiotensin-converting enzyme 2 receptor on the surface of neurovascular cells (i.e., endothelial cells, pericytes, and glial cells), whose dysfunction may result in a wide range of neurological manifestations. Endothelial activation facilitates both venous and arterial thrombotic events, hence the increased risk of ischemic or hemorrhagic stroke. Blood–brain barrier (BBB) impairment determines the loss of immune-privilege leading to inflammatory CNS events [1]. The cytokine storm triggered by the most severe cases of SARS-CoV-2 infection may also induce a neurovascular unit and BBB dysfunction, thus causing indirect CNS damage [2].

Acute cerebrovascular disease has been reported in about 2.8% of COVID-19 patients with an overall estimate of venous and arterial thromboembolic complications between 5 and 15% in some series. Multiple cases of CNS demyelinating diseases have been described in patients with SARS-CoV-2 infection and acute transverse myelitis appeared to be an unexpectedly frequent neurological post-infective complication as well. Acute encephalopathies and encephalitis, presenting with mild to moderate confusion or overt delirium, have been reported in up to 31.8% of hospitalized COVID-19 patients with neurological symptoms. Other manifestations include seizures, cranial nerve abnormalities, and impairment of taste, smell, and vision [3]. Posterior reversible encephalopathy syndrome (PRES) has been reported as a rare occurrence, predominantly in patients with comorbidities and severe infections [4].

We present the case of a young female who was diagnosed with systemic lupus erythematosus (SLE) and active renal disease in September 2020. She was hospitalized and successfully treated with cyclophosphamide and steroid pulses after undergoing a renal biopsy, which revealed class IV lupus nephritis. She later developed proximal deep venous thrombosis of the axillary and subclavian veins from a peripherally inserted central catheter. Laboratory exams revealed a low positive titer of anti-cardiolipin and anti-$\beta_2$glycoprotein-I IgG antibodies which may have contributed to a thrombotic diathesis. After initiating low molecular weight heparin, the patient became oligo-anuric and developed an expanding perirenal hematoma, treated by angiographic embolization, in the previously biopsied kidney. For developing renal insufficiency, she underwent continuous veno-venous hyperfiltration followed by hemodialysis until renal function recovery and spontaneous diuresis resumption. Laboratory exams also indicated a progressive improvement of SLE-related serological abnormalities (C3 0.21→0.84 g/L [0.9–1.8]; C4 0.05→0.15 g/L [0.09–0.36]; anti-dsDNA 2560.0→25.9 IU/mL]). During the recovery phase a surveillance nasopharyngeal swab resulted positive for SARS-CoV-2 and, even in absence of any overt respiratory symptom, laboratory tests revealed a biochemical profile consistent with the viral infection, characterized by increased levels of ferritin (1745 µg/L [10–120 µg/L]), C-reactive

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protein (13.0→58.0 mg/L [< 2.9 mg/L]), and interleukin-6 (18 ng/L [3–7 ng/L]), negative procalcitonin and thrombocytopenia (129×10^9/L [$150–450 \times 10^9$/L]). The patient's blood pressure sharply increased to 180/120 mmHg, and poorly responded to a multitarget antihypertensive therapy based on urapidil and nitroglycerin continuous infusion. Over 24–36 h she developed episodes of tonic–clonic seizures followed by headache and lethargy. The brain magnetic resonance imaging (MRI) (Fig. 1) revealed both vasogenic and cytotoxic edema in frontal, parietal, and occipital lobes as well as the presence of hemorrhagic foci in the right parietal lobe (Fig. 1I), strictly close to hyperintense diffusion weighted imaging (DWI) (Fig. 1G) and hypointense apparent diffusion coefficient (ADC) (Fig. 1H) cortical signal. The patient underwent a strict monitoring without developing signs of respiratory function impairment. Treatment was based on anti-epileptic drugs and maximized anti-hypertensive therapy in order to obtain a tight blood pressure control. This shortly led to a complete resolution of acute cerebral manifestations. During follow-up visits, she presented with a normal neurological exam and good control of epileptic symptoms taking valproic acid. A cerebral MRI performed in May 2021 revealed the almost complete disappearance of the previously observed sub-cortical edematous lesions, with focal degeneration where cytotoxic oedema was previously described (Fig. 1J).

PRES is an acute endotheliopathy characterized by vasogenic edema usually involving the occipital lobes. It can be triggered by various conditions such as systemic infections, autoimmune diseases, renal disorders, eclampsia, hypertensive episodes, and cytotoxic drugs. Key pathogenetic mechanisms include severe hypertensive state with cerebral hyper-perfusion (vasogenic theory), toxin-induced endothelial disfunction (cytotoxic theory), and primary inflammatory response involving T cells and cytokine release (immunogenic theory). Clinical manifestations comprise visual disturbances, epileptic seizures, altered consciousness, headache, nausea, and vomiting.

PRES has been described as a neurological complication associated with COVID-19 in a growing number of case reports since the start of current pandemic [4]. It mainly occurs in the most severe forms of COVID-19 and in patients with diabetes or multiple comorbidities. Currently available data show no clear sex-based differences for PRES in COVID-19 patients although general epidemiologic analysis attests a slightly increased male susceptibility for severe SARS-CoV-2 infections. The most likely pathogenetic mechanisms for PRES in COVID-19 are direct endothelial and neuronal damage and cytokine-mediated vascular injury. Some reports have hypothesized that prolonged mechanical ventilation and immunosuppressants (i.e., tocilizumab) may contribute to PRES onset though targeted anti-cytokine therapy demonstrated to prevent a severe disease course [4].

In most cases, patients present with overt hypertension, altered consciousness, and visual disturbances, although clinical manifestations may sometimes be mild and pressure values only slightly elevated [4]. The most relevant imaging difference between PRES in COVID-19 patients and PRES in other settings appears to be a slightly higher rate of hemorrhage with a comparable proportion of restricted

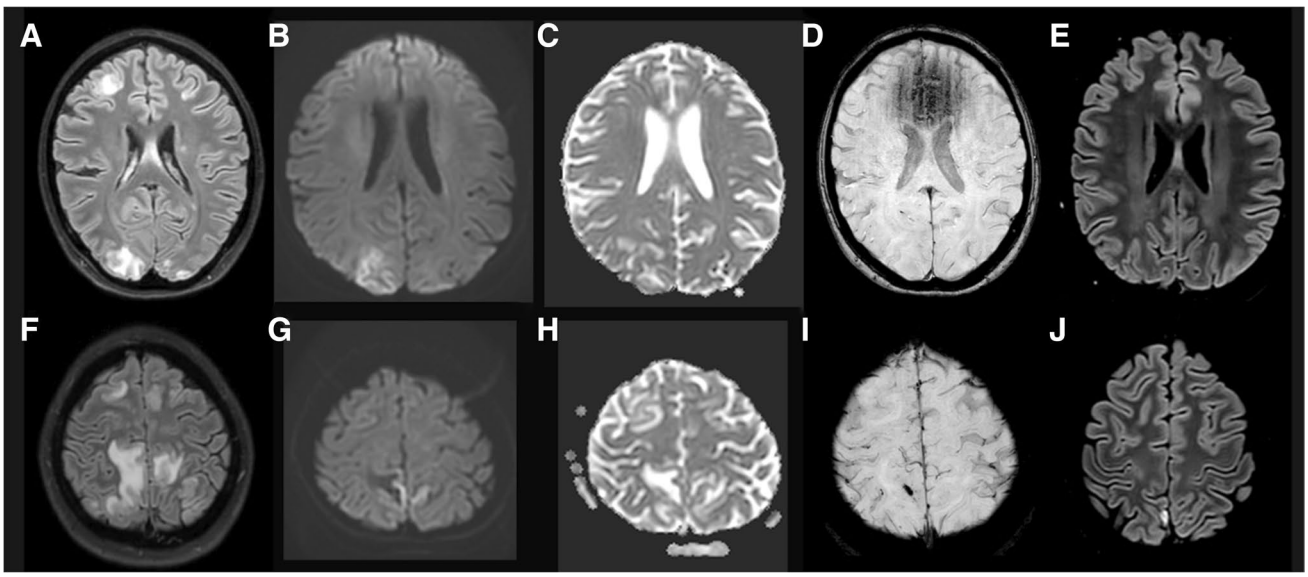

Fig. 1 Vasogenic edema was observed in frontal and occipital lesions (**A**, **B**, and **C**), in absence of any hemosiderin accumulation (**D**), which completely reverted (**E**). The lesion in the right parietal lobe (**F**) was characterized by a strong vasogenic edema with a cytotoxic edema involving the parietal cortex selectively (**G** and **H**). This lesion presented hemosiderin accumulation (**I**) and follow-up imaging disclosed the cortical modification (**J**)

diffusion coefficient. In some cases, a rapid evolution to intraparenchymal hemorrhage has been reported and this attests the precarious balance between a hypercoagulative and pro-hemorrhagic state in patients with COVID-19, with potentially fatal consequences in those with predisposing CNS disorders.

As mentioned earlier, PRES may occur in patients with autoimmune disorders (i.e., SLE) from multiple etiologies such as hypertension, renal failure, and immunosuppressive therapy via fluid retention effect or direct endothelial toxicity. However, given that our patient got infected during a period of decreased SLE disease activity, the onset timing of neurological manifestations suggests that the virus might be the main culprit for the endothelial damage, bearing in mind the preexisting predisposing vascular risk factors. Our patient did not develop respiratory symptoms and PRES was the only clinical manifestation. Two other similar cases of atypical COVID-19 presentation with a PRES have been previously reported in the literature [5], thus expanding our knowledge of potential alternative clinical manifestations in COVID-19.

SARS-CoV-2 has infected millions of people worldwide, often causing severe complications and deaths. In this rapidly evolving phase, where viral knowledge and containment measures are priorities, direct reporting and experienced-based data are essential to obtain as much information as achievable. There is increasing evidence of neurological manifestations during or after COVID-19 supporting the hypothesis of a direct and indirect neurotoxicity of the virus. Further investigations on the underlying pathogenetic mechanisms, potential neurological complications, and atypical presentations of SARS-CoV-2 infection are needed to optimize patient management and improve the prognosis.

Acknowledgements Authors would like to express special thanks to Dr. M. Anglani who has contributed to revision and selection of MRI images.

Availability of data and material All data relevant to the clinical case are included in the article.

Declarations

Ethical approval Not applicable.

Consent for publication Patient informed consent for publication was obtained on 21 December 2020.

Competing interests The authors declare no competing interests.

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