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COVID-19-associated encephalitis successfully treated with combination therapy

Eric Freire-Álvarez a, Lucía Guillén b, Karine Lambert c, Ana Baidez a, Miguel García-Quesada a, María Andreo b, Jordi Alom a, Mar Masiá b, Félix Gutiérrez b,⇑

⇑Corresponding author at: Unidad de Enfermedades Infecciosas, Hospital General Universitario de Elche, Alicante, Spain.
E-mail address: gutierrez_fel@gva.es (F. Gutiérrez).

a Neurology Department, Hospital General Universitario de Elche, Alicante, Spain
b Infectious Diseases Unit, Hospital General Universitario de Elche and Universidad Miguel Hernández, Alicante, Spain
c Magnetic Resonance Imaging Unit, Radiology Department, Hospital General Universitario de Elche, Alicante, Spain

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Background: Acute encephalitis can occur in different viral diseases due to infection of the brain or by an immune mechanism. Severe novel coronavirus disease 2019 (COVID-19) is associated with a major immune inflammatory response with cytokine upregulation including interleukin 6 (IL-6). We report a case presenting with acute encephalitis that was diagnosed as having severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection with hyperinflammatory systemic response and recovered after therapy with immunoglobulins and cytokine blockade.

Case report: A 39-year-old man was brought to the Emergency Department with drowsiness, mental disorientation, intermittent fever and headache. A brain magnetic resonance imaging showed extensive involvement of the brain including cortical and subcortical right frontal regions, right thalamus, bilateral temporal lobes and cerebral peduncles, with no leptomeningeal enhancement. Cerebrospinal fluid (CSF) showed a leukocyte count of 20/μL (90% lymphocytes), protein level of 198 mg/dL, and glucose of 48 mg/dL. SARS-CoV-2 was detected in nasopharyngeal swabs by reverse-transcriptase-PCR (RT-PCR) but it was negative in the CSF. Remarkable laboratory findings in blood tests included low lymphocyte count and elevated ferritin, IL-6 and D-dimer. He had a complicated clinical course requiring mechanical ventilation. Intravenous immunoglobulins and cytokine blockade with tocilizumab, an IL-6 receptor antagonist, were added considering acute demyelinating encephalomyelitis. The patient made a full recovery, suggesting that it could have been related to host inflammatory response.

Conclusion: This case report indicates that COVID-19 may present as an encephalitis syndrome mimicking acute demyelinating encephalomyelitis that could be amenable to therapeutic modulation.

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Background

The current pandemic of coronavirus disease 2019 (COVID-19) poses major challenges to clinicians. Although patients usually present with respiratory symptoms, a growing number of extrarespiratory manifestations are being described as the disease spreads throughout the world. Acute encephalitis can be the main manifestation of different viral infections, either directly or by an immune-mediated mechanism. Postmortem and experimental studies have shown that both severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) could enter the brain and spread to various areas, including thalamus and brain stem [1,2]. SARS-CoV has additionally shown to cause immunopathological brain damage [3]. SARS-CoV-2, the agent causing the novel coronavirus disease 2019 (COVID-19), is associated with a major immune inflammatory response with abundant neutrophils, lymphocytes, macrophages, and cytokine up-regulation amenable to therapeutic target [4,5].

Case report

A 39-year-old man that was brought to the Emergency Department in the second week of March 2020 due to mental disorientation and inconsistent language disorder. During the previous two weeks the patient had felt fatigue and malaise, and five days before he developed intermittent fever up to 39 °C with mild headache. At the time of admission, neurological examination revealed a
tendency to drowsiness, minimal stiff neck and paraphasia. Initial laboratory data included a white blood cell count of 4.400/µl (normal value, 4.00–11.00/µl) with mild lymphopenia of 1.10/µl (normal value, 1.50–4.50/µl). A brain computed tomography (CT) scan without contrast and a chest X-Ray were normal. Lumbar puncture (LP) revealed clear cerebrospinal fluid (CSF) with a leukocyte count of 20/µl (90% lymphocytes), 0 red cells/µl, protein level of 198 mg/dl (normal value, 12.00–60.00 mg/dl), and glucose of 48 mg/dl (normal value, 45.00–80.00 mg/dl). Gram staining was negative. The patient was treated empirically with intravenous acyclovir, pending on the microbiological results. Over the following hours the level of consciousness and the confusional state deteriorated. A polymerase-chain-reaction (PCR) multiplex in CSF for several neurotropic viruses including cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, human herpesvirus 6, human parechovirus and varicella-zoster virus showed negative results. Given the COVID-19 pandemic in Spain, this diagnosis was considered and, unexpectedly, the determination of SARS-CoV-2 by reverse-transcriptase-PCR (RT-PCR) assay in nasopharyngeal swabs was positive, subsequently confirmed in a second sample. RT-PCR for SARS-CoV-2 in the CSF was negative. Serological tests for HIV, Treponema pallidium and Borrelia burgdorferi were negative. A brain magnetic resonance imaging (MRI) 1.5 Tesla showed a hyperintensity at the cortical and subcortical right frontal regions, right thalamus and mammillary body, bilateral temporal lobes and cerebral peduncles, with no leptomeningeal enhancement (Fig. 1). Even in the absence of symptoms, a chest CT scan was performed showing bilateral findings typical of COVID-19 located in the posterior segment of the upper lobe, the right lower lobe and the lingula (Fig. 2). Antiviral therapy with lopinavir/ritonavir (400/100 mg bid) and subcutaneous interferon beta-1b (250 mcg/48 hours) were started. Three days after admission the patient remained febrile and his clinical condition worsened. Intravenous immunoglobulins (0.4 gr/kg/day for 5 days) were added considering acute demyelinating encephalomyelitis. Over the next few days he developed progressive pulmonary infiltrates and was transferred to intensive care with respiratory failure requiring mechanical ventilation. Remarkable laboratory findings included: ferritin, 866 ng/ml (17.9–464.0), IL-6, 135.7 pg/ml (0.00–7.00), D-dimer, 1.93 mg/L (0.00–0.50). Treatment with intravenous tocilizumab (400 mg/24 hours for 3 days) followed. His condition improved within five days and mechanical support could be discontinued. Consecutive nasopharyngeal SARS-CoV-2 remained positive during the first two weeks of hospitalization. A second MRI performed on the 28th day of admission showed an outstanding improvement of the brain lesions (Fig. 3). Thirty days after admission, the patient is in good clinical condition, although a mild confusional state remains. SARS-CoV-2 is no longer detected by RT-PCR in nasopharyngeal swabs.

Discussion and conclusions

As the COVID-19 pandemic continues, neurological manifestations of the disease have become increasingly apparent and sporadic cases of encephalitis have already been reported [6,7]. During other pandemics of respiratory pathogens, including H1N1 influenza, there were similar reports of patients with neurological complications, including cases of encephalitis [8,9].

In a nationwide surveillance study to investigate the spectrum of neurological and psychiatric complications of COVID-19 across the UK, altered mental status including encephalopathy or encephalitis and primary psychiatric diagnoses was the second most common neuropsychiatric complication, often occurring in younger patients. Seven of the 153 cases notified to the registry presented with encephalitis [10]. Among 1760 patients with COVID-19 admitted to Bergamo, Italy, 137 (7.8%) developed a neurologic complication [11]. Based on clinical characteristics, CSF data and neuroimaging, the diagnosis of encephalitis was established in five patients, among whom one was herpes simplex virus 1-related, one necrotizing encephalitis, and two patients had SARS-CoV-2 detected in CSF by RT-PCR. Despite most of the patients with altered mental in this cohort had a brain MRI performed, they did not observe any case of acute disseminated encephalomyelitis, an immune mediated disease that often occurs following viral infections [12].

The case reported here indicates that COVID-19 may present as an encephalitis syndrome mimicking acute demyelinating encephalomyelitis that could be amenable to therapeutic modulation. Indeed, the patient recovered after therapy with immunoglobulins and cytokine blockade. The exact pathogenic mechanism involved in the neurological injury in this case is
difficult to ascertain due to the lack of brain pathology samples. Although it might have been due to direct viral infection of neuronal cells, as it has been shown by brain necropsy in different cases of SARS-CoV [3,13,14], it could also be related to a specific host inflammatory immune-mediated response. The negative RT-PCR CSF results for SARS-CoV-2 along with the hyperinflammatory systemic response observed and the impressive findings in the MRI after therapy with immunoglobulins and tocilizumab suggest an acute disseminated encephalomyelitis.

**Ethical approval and consent to participate**

No approval by the Institutional Review Board of Hospital Universitario de Elche was required for this manuscript. Informed consent was obtained from the patient for publication of this case report.

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**CRediT authorship contribution statement**

Dr Freire and Dr Guillen: conceptualization and writing; Dr Baidez, Dr Garcia Quesada, Dr Andreo, Dr Lambert and Dr Alom: review and editing; Dr Masiá and Dr Gutierrez: supervision, writing, review and editing.
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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