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Clinical report

Encephalitis as a neurological manifestation of COVID-19

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A B S T R A C T

Introduction: In the context of the global COVID-19 pandemic, the different clinical manifestations of this infection pose a challenge for healthcare professionals. Respiratory involvement, the main symptom of SARS-CoV-2 infection, means that other manifestations, such as neurological, take a back seat, with the consequent delay in diagnosis and treatment.

Material and methods: All COVID-19 patients admitted with neurological symptoms or diagnosed with encephalitis since March 2020 in a tertiary hospital in Zaragoza, Spain.

Results: Two patients with COVID-19 infection confirmed by nasopharyngeal PCR and whose clinical picture consisted of neurological alterations compatible with encephalitis. Cerebrospinal fluid (CSF) microbiology was negative for bacteria and viruses, including SARS-CoV-2 but, given the clinical suspicion of encephalitis due to the latter, antiviral treatment with immunoglobulins and plasmapheresis was started early. Despite this, the evolution was not satisfactory.

Conclusions: COVID-19 encephalitis is a recently described clinical entity, whose pathophysiology is still unknown and no treatment with clinical evidence is available to date.

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Encefalitis como manifestación neurológica del COVID-19

R E S U M E N

Introducción: En el contexto de la pandemia mundial por COVID-19, las distintas manifestaciones clínicas de esta infección suponen un reto para los profesionales sanitarios. La afectación respiratoria, síntoma principal de la infección por SARS-CoV-2, hace que otras manifestaciones, como las neurológicas, pasen a un segundo plano, con el consecuente retraso en el diagnóstico y tratamiento.

Material y métodos: Todo paciente COVID-19 que ha ingresado con sintomatología neurológica o diagnosticado de encefalitis desde Marzo de 2020 en un hospital de tercer nivel en Zaragoza, España.

Resultados: Dos pacientes con infección COVID-19 confirmada por PCR nasofaríngea y cuyo cuadro clínico consistía en alteraciones neurológicas compatibles con encefalitis. La microbiología del líquido cefalorraquídeo (LCR) fue negativa para bacterias y virus, incluido el SARS-CoV-2 pero, ante la sospecha clínica de encefalitis por este último, se instauró tratamiento antiviral, con inmunoglobulinas y plasmaderesis de forma precoz. A pesar de ello la evolución no fue satisfactoria.

Conclusiones: La encefalitis por COVID-19 es una entidad clínica descrita recientemente, cuya fisiopatología aún se desconoce y no se dispone, hasta la fecha, de un tratamiento con evidencia clínica.

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Around mid-December 2019, the first cases of pneumonia and respiratory distress were reported in Wuhan, China, as a result of infection by a new coronavirus (SARS-CoV-2), which in the following months was to become the largest epidemic in recent years in living memory.1,2

Coronaviruses are common and widely distributed, causing upper respiratory tract infections in most cases. The clinical manifestations are similar to the flu, and the most common symptoms
are fever (90%), cough and myalgias (50%) and headache (10%). Some more specific symptoms of SARS-CoV-2 infection are anosmia and ageusia, which have been considered early symptoms and affect 60% of patients.\(^1\)

The development of bilateral pneumonia, respiratory superinfections or respiratory distress syndrome are the most common complications; however, other extrapulmonary involvement, such as cardiomyopathy or encephalitis, has also been reported, although less frequently. Besides, they entail a complicated diagnosis and a poor prognosis.\(^1,2\)

We report the case of two patients with SARS-CoV-2 infection whose main involvement was neurological.

**Case 1**

52-year-old male, a native of the Dominican Republic, resident in Spain for eight years, and with no medical history of interest. The patient came to the emergency department reporting a 4-day history of fever and headache and neurological symptoms consisting of gait disturbances and dysarthria of sudden onset, just 2 h before. Physical examination showed a body temperature of 36 °C, baseline oxygen saturation of 95%, Glasgow 15, bradypnea and dysarthric speech, with no other obvious neurological focus. Laboratory tests showed a C-reactive protein concentration of 40.5 mg/L (normal range 0.1–5 mg/L), white blood cells 6.6 × 10^9/L (76.3% neutrophils and 7.42% lymphocytes). A brain computed tomography (CT) scan was performed, which showed no abnormalities. The rapid test for influenza A and B viruses and respiratory syncytial virus was negative, as was the legionella and pneumococcus urine antigen test. SARS-CoV-2 disease was confirmed after polymerase chain reaction (PCR) analysis of nasopharyngeal swab and was admitted to the infectious disease unit pending study completion.

Three hours after admission, he presented with a generalized tonic-clonic seizure, with sustained post-ictal clouding of consciousness, for which he was admitted to the Intensive Care Unit (ICU) and required orotracheal intubation and mechanical ventilation. A lumbar puncture was performed to obtain cerebrospinal fluid (CSF), which was clear in appearance and whose biochemistry and microbiology were completely normal. Given the suspicion of neurological involvement by SARS-CoV-2, its isolation in the CSF was requested, which was negative. Antibiotic treatment with levetiracetam and antibiotic treatment with ceftriaxone were initiated. In addition, antiviral treatment with lopinavir/ritonavir and hydroxychloroquine and \(^8\)-interferon was started and discontinued early, according to the hospital protocol in place at the time.

24 h after admission to the ICU he developed bilateral mydriasis. The new brain CT scan showed predominately right-sided cortico-subcortical hypodense areas in the sulci of the frontal convexity, probably of ischaemic origin, and signs of diffuse cerebral oedema (fig. 1). An intracranial cerebral pressure (ICP) sensor showed intracranial hypertension (60 mmHg) and treatment was started with thiopental perfusion (2 g/12 h), corticosteroid pulses (methylprednisolone 1 g/24 h) and plasmapheresis sessions for seven days.

A new CT scan of the brain showed multiple hyperdense lesions, compatible with autoimmune disseminated leukoencephalopathy. Given the normalization of ICP figures, the barbiturate coma therapy was discontinued. The electroencephalogram (EEG) was suggestive of poor prognostic criteria and transcranial Doppler data were compatible with brain death. After the consensus of the multidisciplinary medical team with the family, life support treatment was limited, resulting in the death of the patient.

**Case 2**

A 70-year-old man with a history of cardiovascular risk factors (hypertension, DM, dyslipidaemia, and former smoker), moderate alcohol consumption, stage IIIA chronic renal failure, atrial fibrillation (chronically anticoagulated with acenocoumarol), COPD, and apnoea-hypventilation syndrome, night CPAP carrier.

The patient had been diagnosed with SARS-CoV-2 infection during the epidemiological study after contact with a positive case. He came to the emergency department three days later with deterioration of general condition, instability and difficulty standing upright. During the clinical examination, oxygen saturation was 96%, with no work of breathing, and cardiopulmonary auscultation did not reveal pathological sounds except for an irregular heart rhythm, previously known. Brain CT without acute findings. He was admitted to the hospital ward for study and treatment with ceftriaxone, azithromycin, and methylprednisolone at doses of 20 mg/24 h IV.

He was assessed by the Neurology Department on several occasions, whose clinical assessment was an episode of delirium or abstinence from alcohol consumption. CT and brain CT angiography were repeated, showing no abnormalities. There was a progressive neurological worsening of the patient, with the onset of a Cheyne-Stokes respiratory pattern and desaturation up to 88%. A pulmonary CT angiography was performed, which showed small-vessel pulmonary embolisms, for which the dose of subcutaneous enoxaparin was increased to 80 mg/12 h, the patient was intubated and transferred to the Intensive Care Unit.

A lumbar puncture was performed, and CSF was obtained, with clear fluid and normal pressure. Empirical treatment with acyclovir, ceftriaxone, and ampicillin was initiated and corticosteroid treatment was maintained. Biochemistry, microbiology, and PCR for SARS-CoV-2 in CSF were negative. The EEG showed a non-convulsive status epilepticus that resolved with the start of treatment with levetiracetam, with the following EEGs showing slowed activity, but without signs of status epilepticus. Magnetic resonance imaging (MRI) showed signs of small vessel encephalopathy which did not justify the clinical condition. In coordination with the neurology department, 1 g of intravenous methylprednisolone bolus was administered over 72 h, with no improvement. The patient remained in hospital for several weeks and was transferred to the long-stay unit where he died.

Since the beginning of the pandemic, extensive data on the main manifestations of COVID-19 have been published. Among all of them, neurological involvement seems to be uncommon, although with very varied manifestations and different pathophysiology.

The most common neurological manifestations are usually mild, such as headache, anosmia, and ageusia. However, there are other manifestations with greater clinical significance and, above all, greater morbidity and mortality, including cerebral ischaemic processes, encephalitis, alterations in the level of consciousness or memory and polyneuropathies.\(^3\)

Encephalitis is defined as the occurrence of an acute and sustained encephalopathy lasting more than 24 h (including lethargy, irritability, or behavioural changes) and evidence of brain inflammation, manifested by fever, vomiting, seizures, EEG abnormalities and/or compatible CT or MRI.\(^2,4\)

The most common aetiology is viral, specifically secondary to the herpes simplex virus. Nevertheless, other viruses such as varicella zoster virus (VZV), Epstein Barr virus (EBV) or cytomegalovirus (CMV) have also been isolated from CSF, but less frequently. The emergence of SARS-CoV-2 over the past year has led to the occurrence of new cases of encephalitis due to this cause; however, the diagnosis is based on clinical and/or neuroimaging findings, as this virus has only been isolated in CSF in a very specific manner and with extremely limited means, such as reverse transcription PCR.\(^2,5,6\)
Although the new coronavirus is not, a priori, a neurotropic virus, but rather its primary target is the nasopharyngeal epithelium, the pathophysiology by which neurological involvement occurs is not entirely clear, and there could be several mechanisms involved. Firstly, transient virus spread to the CSF with extremely low titres is contemplated, which makes virus isolation difficult. Another option, which according to experts is the most plausible, is immune-mediated encephalitis: SARS-CoV-2 would produce an immune response and an activation of the cytokine cascade (complement, IL-6, IL-10, TNF, coagulation, etc.) leading to the brain oedema and swelling responsible for the clinical condition.\textsuperscript{1,2,4,5,7} Acute necrotising encephalopathy (ANE) is a rare neurological complication caused by cytokine storm and damage to the blood-brain barrier, reported after severe viral infections. It presents with necrotic lesions with perilesional enhancement on brain CT.\textsuperscript{2} In any case, life support and treatment of intracranial hypertension are paramount. Given the existing hyperinflammatory state, the use of intravenous immunoglobulins and corticosteroids, or even plasmapheresis, could promote viral clearance and be useful. Cyclophosphamide or rituximab are treatments with significant side effects, which is why they have not been used to date. No treatment has shown proven efficacy.\textsuperscript{2,3,8} Due to the increasing incidence of COVID-19, its neurological manifestations are becoming more and more common. There is, therefore, an urgent need to understand and diagnose neurological syndromes as early as possible in order to optimise treatment.

Conflict of interests
The authors declare no conflict of interest.

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