



Acute meningoencephalitis associated with SARS-CoV-2 infection in Colombia

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Abstract

We present the case of a patient in the third decade of life, with asthma as comorbidity, who presented to the emergency department due to odynophagia, dyspnea, and cough of 2 days of evolution, later developing acute ventilatory failure requiring orotracheal intubation. The high-resolution chest tomography study showed consolidation due to a pneumonic process towards the posterior segment of the right lower lobe with areas of ground-glass infiltrates with a peripheral distribution. During the clinical course, the patient presented multiple seizure episodes that met the criteria for status epilepticus with MRI compatible with changes due to leptomeningitis. Given symptoms and thorax imaging, tests for SARS-CoV-2 ensued, with both positive RT-PCR in bronchoalveolar lavage and cerebrospinal fluid for the virus also positive. RT-PCR multiplex panel of meningitis/encephalitis results negative for 14 common organisms. A diagnosis of acute meningoencephalitis associated with COVID-19 was considered, with an adequate response to corticosteroid management; to our knowledge, this is the first adult patient with CNS involvement and CSF positive test in Latin America.

Keywords COVID-19 · SARS-CoV-2 · Encephalitis · Seizures · Colombia

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic (Dhama et al. 2020) may cause neurological consequences not previously reported (Vargas-Gandica et al. 2020). These features may be a combination of nonspecific complications of systemic disease (Dhama et al. 2020), the effects of direct viral infection, or inflammation of the central nervous system (CNS) and vasculature, which can be para-infectious or post-infectious. Compromise of both the CNS and peripheral nervous systems (PNS) has been demonstrated in patients with severe and non-severe COVID-19 (Ellul et al. 2020).

Although SARS-CoV-2 antigens are detected in different CNS structures, and reactivity by immunohistochemistry in brain sections of autopsies has been reported, the pathophysiology of CNS involvement is still unclear. The endothelial lining of the cerebral vasculature via their angiotensin-converting enzyme (ACE) II receptors tropism or the olfactory nerve, tracts and olfactory striae, towards the piriform cortex are considered as the main possible entry routes (Davies et al. 2020).

On March 4, 2020, at Beijing, China, the first case of CNS involvement with cerebrospinal fluid (CSF) positive

for SARS-CoV-2 by sequencing was confirmed (Zhang et al. 2020). As the COVID-19 pandemic progressed, laboratory data showed that the overall yield of RT-PCR in CSF was low, and, despite many patients exhibiting signs of CNS involvement, most test were negative, making the diagnosis challenging. The detection of SARS-CoV-2 in CSF is relevant due to the steroids use as part of the standard management, which may be contraindicated in other conditions requiring antimicrobial therapy. We described a case of meningoencephalitis with positive CSF for SARS-CoV-2 in Colombia.

Case

We present the case of a 26-year-old female health worker with a history of asthma, who presented odynophagia, dyspnea, and cough in the last day before admission, without symptoms improvement using salbutamol (Fig. 1). The next day, she arrived at the emergency department due to self-limited diarrhoea and worsening respiratory symptoms. She was admitted with bronchial obstruction, desaturation, and tachycardia. Chest X-ray showed bronchoalveolar opacities mainly at the right base, with metabolic acidosis, severe oxygenation impairment, and leukocytosis. She developed type I ventilatory failure and was referred to the Intensive Care Unit (ICU). In Fig. 1, a timeline of the main events of

the case is presented, including the major clinical findings, studies and management.

At 23 h in ICU, without a prior history of seizures or epilepsy, the first episode of tonic posture and clonic movements of four limbs ensued without sphincter relaxation and was controlled with midazolam. A simple brain MRI with contrast showed postictal oedema (Fig. 2), and a CSF sample was consistent with an inflammatory profile (Table 1). Given no other explanation for the patient illness and new convulsive episodes with CSF changes (pleocytosis and hyperglycorrachia), SARS-CoV-2 infection was assessed. New samples from bronchoalveolar lavage and CSF were drawn for RT-PCR analysis (Table 1) plus MRI of CNS and thorax CT-scans (Fig. 2), resulting positive for SARS-CoV-2 (Table 1). This RT-PCR test for SARS-CoV-2 detection uses the primers and probes of the Charité Berlin protocol (Germany) for RdRp and E genes identification (Corman et al. 2020). Additionally, it detects the nucleocapsid gene using the primers and probes proposed in the China Centers for Disease Control and Prevention (CDC) protocol (China CDC 2020).

Dexamethasone 8 mg every 6 h was initiated and received for 5 days. MRI results show generalized cortical edema, while pulmonary CT scan revealed pneumonic opacities at the right base with a ground-glass pattern. In the next few days, the patient continued improving oxygenation parameters, with lowering of severity markers and inflammation. As the corticosteroid therapy concluded, sedation and

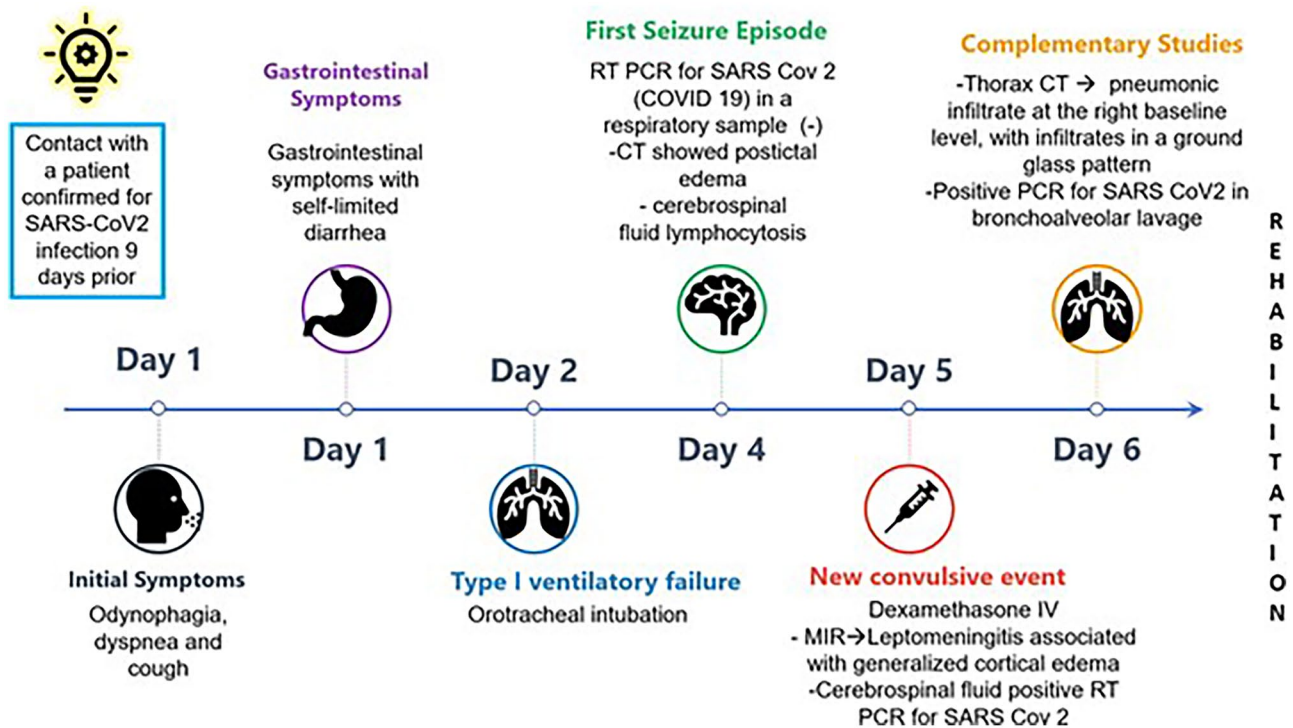
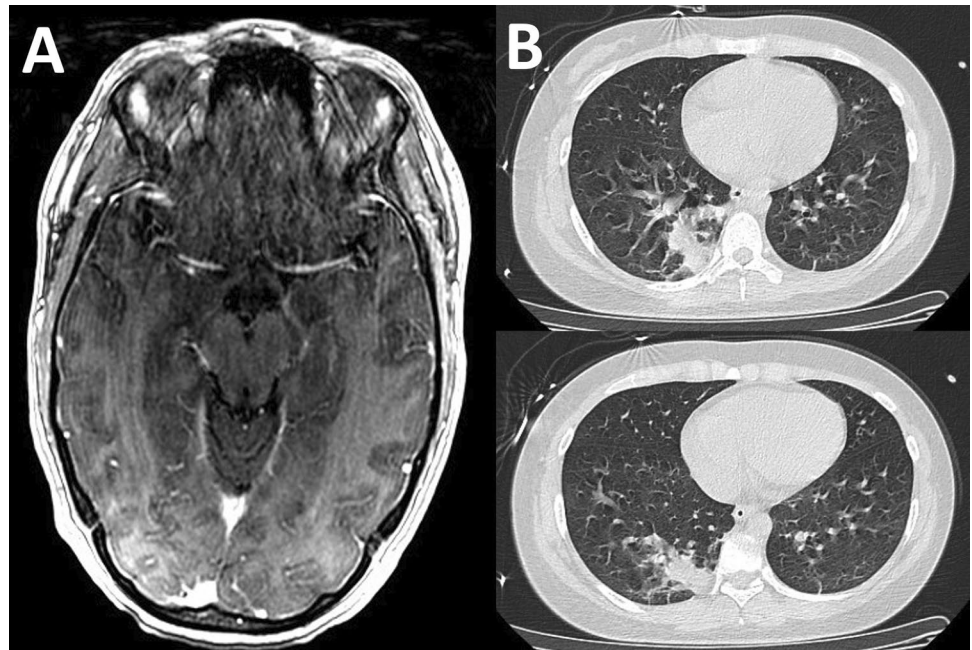


Fig. 1 Timeline of the case

Fig. 2 Simple brain MRI with contrast showing postictal oedema (A), and thorax CT-scans of the patient (B)



antiepileptics were withdrawn with no seizures and adequate clinical evolution, being discharged after 34 days of hospitalization (a total of 11 days at the ICU). The rehabilitation process began with overall good results. A follow-up electroencephalogram after 1 month of discharge showed normal findings (Fig. 3).

Discussion

Increasing evidence shows that neurotropism is a common feature of human CoVs, such as HCoV-229E, HCoV-OC43, but also SARS-CoV, MERS-CoV and SARS-CoV-2 (Pene et al. 2003). Viral antigens are detected in the brain stem; the infected regions included the nucleus of the solitary tract and the nucleus ambiguus. In our case, although SARS-CoV-2 was not detected on a pathological tissue from CNS, no other infectious agent was identified, and the SARS-CoV-2 RNA was detected in CSF, we presume this to be the causative agent. Recent findings suggest that severity and mortality may be due to dysfunction of the cardiorespiratory centre in the brainstem (Pene et al. 2003). Neurological symptoms can be divided into 3 categories (Mao et al. 2020): CNS signs and symptoms: headache, vertigo, altered consciousness, ataxia, seizure, stroke; peripheral nervous system signs and symptoms: hypogeusia, hyposmia, neuralgia/neuropathy, Guillain Barre syndrome; and symptoms of skeletal muscle injury: Myalgia + Elevated CPK levels > 200 U/L.

Three radiological patterns are described in severe COVID-19 infection at the CNS level: signal abnormalities located in the medial temporal lobe, non-confluent multifocal white matter (WM) hyperintense lesions on FLAIR

and diffusion with variable enhancement, associated with extensive and isolated WM microhaemorrhages (Kremer et al. 2020).

Regarding meningoencephalitis, this is associated with headache, fever and nuchal stiffness. Encephalitis corresponds to the underlying involvement of the brain parenchyma, including behavioural changes, neurological targeting, altered state of consciousness, and seizures. The CSF shows hyperproteinrrachia, pleocytosis, and euglycorrhachia (Kremer et al. 2020). A study on CSF samples during the beginning of the France COVID-19 epidemic (Destras et al. 2020) showed a low proportion of SARS-CoV-2 positive patients (2/622), with high viral loads (Ct value < 25) at respiratory samples, but low load in CSF. By ruling-out blood contamination by traumatic lumbar puncture in a high viral load pneumonia setting (Faico-Filho et al. 2020), the diagnosis of SARS-CoV-2 invasion of the CNS is plausible. In most meningoencephalitis, a high load, particularly in blood, is a prerequisite of direct invasion of the CNS; hence, in our patient, the coincidence of both is consistent. As most reports coincide, the CNS pathogenesis in COVID-19 is more directly related to the immune response than for a direct neural cytopathic effect (Lucchese 2020). In Latin America, only one report from Argentina described the presence of SARS-CoV-2 in a CSF sample (Mohammadi et al. 2020).

The importance of clinically suspected SARS-CoV-2 infection in people at high risk, such as healthcare workers, is highlighted. In the presence of initial tests performed by negative nasopharyngeal swab, if the clinical suspicion is high and the existence of a false negative is possible, and there is extrapulmonary involvement (as in the

Table 1 Laboratory findings of the patient

Test	Finding	Reference values
Cerebrospinal fluid		
Aspect	Transparent	
pH	8.0	
Density (g/mL)	1.015	1.0063–1.0075
Glucose (mg/dl)	90.7	40–70
Proteins (mg/dL)	32.3	15–45
Leukocytes (cells/mL)	34	0–8
Neutrophils (%)	50	
Lymphocytes (%)	50	
Red blood (cells)	0	
Multiplex PCR meningeal panel		
<i>Cryptococcus neoformans/C. gattii</i>	Negative	Negative
<i>Escherichia coli</i> K1	Negative	Negative
<i>Haemophilus influenzae</i>	Negative	Negative
<i>Listeria monocytogenes</i>	Negative	Negative
<i>Neisseria meningitidis</i>	Negative	Negative
<i>Streptococcus agalactiae</i>	Negative	Negative
<i>Streptococcus pneumoniae</i>	Negative	Negative
Cytomegalovirus	Negative	Negative
Enterovirus	Negative	Negative
Herpes simplex virus 1	Negative	Negative
Herpes simplex virus 2	Negative	Negative
Human herpes virus 6	Negative	Negative
Human parechovirus	Negative	Negative
Varicella zoster virus	Negative	Negative
RT-qPCR* for SARS-CoV-2 at samples from		
Bronchoalveolar lavage	Positive, Ct < 25	Negative
Cerebrospinal fluid	Positive, Ct > 36	Negative

*Samples for RT-qPCR were processed by an in-house protocol in the departmental public health laboratory, “Caldas Protocol,” validated by the National Institute of Health of Colombia for COVID-19 laboratory confirmation. The test evaluated the presence of E, N, RdRp SARS-CoV-2 genes in the CFX96 Touch™ BIORAD RT-PCR system after sample quality controls and RNA extraction. The positive RT-qPCR for SARS-CoV-2 in bronchoalveolar lavage by amplification of the three genes (RdRp, N y E) in both replicates confirmed the diagnosis of COVID-19 pneumonia with a high viral load according to a cycle threshold (Ct) < 25 for all genes. CSF preanalytical steps in both duplicates result in an RNA concentration of 13.6 ng/μL with a ratio 260/280 of 1.8 deemed adequate for downstream analysis. CSF was positive for SARS-CoV-2 in both duplicates with a late Ct value for N gene (Ct > 36); cytochemical analysis of sample revealed no red blood cells in CSF; hence, traumatic lumbar puncture was ruled out

present case, the CNS), a differential diagnosis should be considered for meningeal infection by another pathogen. Once this is ruled out, SARS-CoV-2 should be assessed. Although CSF can be negative, testing SARS-CoV-2 at bronchoalveolar lavage samples is relevant (Patrucco et al. 2020; Taton et al. 2020). The detection of SARS-CoV-2 in the CSF by PCR or the evaluation of intrathecal antibodies’ synthesis seems to be uncommon; less than 7% of the tests performed were positive in patients with neurological manifestations (Lewis et al. 2021).

Most COVID-19 patients with meningoencephalitis improved after corticosteroid treatment (Huo et al. 2021).

Considering SARS-CoV-2 at the CSF as part of the differential diagnosis is key before beginning intravenous corticosteroids. When upper respiratory samples are negative, low respiratory tract samples are unavailable, and there is no other pathogen that explains the neurological signs and symptoms, CSF should be processed for a high sensibility RT-qPCR assay (three gene targets, sensibility ~ 100%) for SARS-CoV-2 detection (Etievant et al. 2020). When ruling out other causes, it is prudent to consider testing for SARS-CoV-2 also in bronchoalveolar lavage. Such samples are sensitive for SARS-CoV-2 infection (Mohammadi et al. 2020).

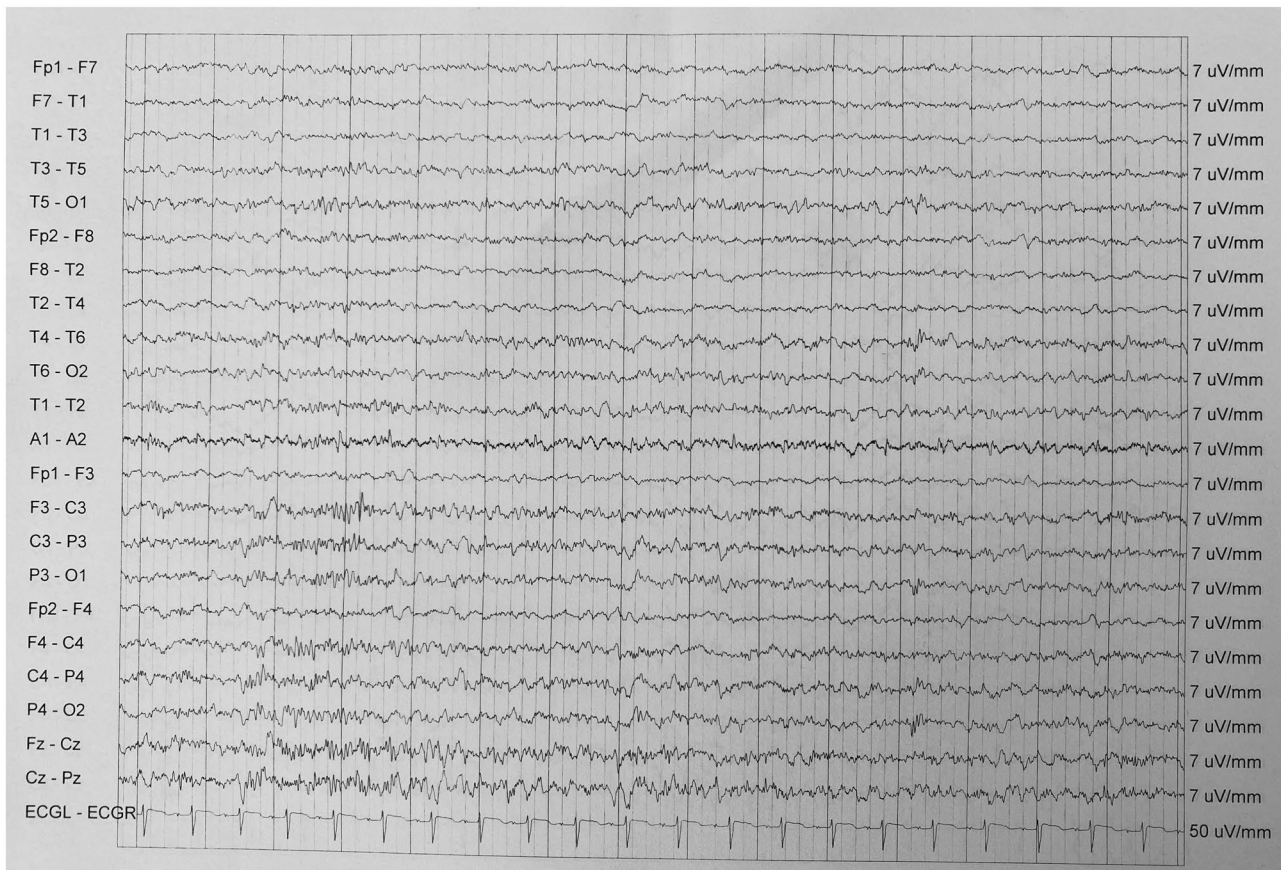


Fig. 3 Electroencephalogram of the patient at a follow-up, at 1 month after discharge

This case is relevant because it shows that the unconscious patients in the current context are potentially infected by SARS-CoV-2, as presumed. To end the pandemic of SARS-CoV-2/COVID-19, its diagnosis must be prompt and not overlook any findings. It should be kept in mind that encephalitis symptoms may be the first indication to find the hidden SARS-CoV-2 infection in some patients.

Author contribution MAPT, JSHB, DDM, and AJRM conceived the report. YO, DDM, AE, JJOM, collected data, analysed and interpreted clinical data. MOR analysed CSF with RT-PCR for SARS-CoV-2 diagnosis. JSHB, DDM, AJRM wrote the first draft. JSHB, DDM, AJRM, reviewed the literature. All authors approved the subsequent draft versions. All authors approved the final submitted version.

Declarations

Ethics approval and consent to participate Written consent from the patient was obtained for publication.

Conflict of interest We declare that we have no competing interests, except that the first author is the reported case.

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