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Coronavirus Pandemic

SARS-CoV-2 associated encephalitis

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Abstract

Introduction: In addition to known systemic manifestations, coronavirus disease (COVID-19) can cause serious neurological manifestations as a result of damage to the central and peripheral nervous system.

Case report: A 62-year-old male with medical history of arterial hypertension and type 2 diabetes mellitus was admitted to the hospital, complaining of high fever, fatigue, cough, and disturbed mental state. He was diagnosed with COVID-19, had fever of up to 38 °C 7 days before admission, dry cough, and became disoriented and psychotic after 5 days. The chest X-ray and computed tomography (CT) of the head were normal. Following a lumbar puncture, the patient was diagnosed with encephalitis based on clinical and laboratory findings (pleocytosis and hyperproteinorachia in cerebrospinal fluid (CSF)). CSF was checked with the polymerase chain reaction meningitis-encephalitis panel which excludes the more common viral or bacterial causes of encephalitis. Anti-edematous, anti-inflammatory, anticoagulant, gastroprotective, and other symptomatic medications were administered. Ataxic gait was the only focal neurological abnormality identified during neurological assessment. The chest CT did not reveal COVID-19 pneumonia and brain magnetic resonance imaging revealed only cortical reductive brain alterations. The COVID-19 swab test after 10 days was negative. The patient was recovered and released from hospital treatment with normal physical findings and without neurological abnormalities.

Conclusions: The diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encephalitis can be challenging, and it is usually based on the exclusion of other etiological agents of brain infections.

Key words: SARS-CoV-2; neurological manifestations; encephalitis.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Most COVID-19 infected patients experience no symptoms or a mild flu-like syndrome. However, some patients, particularly unvaccinated or immune compromised patients, develop pneumonia. In severe cases, patients may develop acute respiratory distress syndrome (ARDS); multiple organ failure; and, less frequently, the symptoms may involve the nervous system [1]. SARS-CoV-2 neurological manifestations are caused by damage to the central and peripheral nervous systems (PNS); and they include headache, encephalopathy, skeletal muscle involvement, acute polyradiculoneuropathy, acute cerebrovascular events, meningitis, encephalitis, and acute disseminated encephalomyelitis. It is believed that neurological problems are more prevalent in severe cases of SARS-CoV-2 infection [2,3]. The term "encephalitis" refers to an inflammation of the brain parenchyma that results in severe neurological alterations that are primarily brought on by viruses. Clinical symptoms of encephalitis include disorientation, altered or decreased consciousness, fever, headache, seizures, and abnormal movements. A combination of laboratory, neuroimaging, and electrophysiological results is typically used to diagnose encephalitis. These findings may include blood tests, lumbar punctures, computed tomography (CT) scans, electroencephalograms (EEG), and magnetic resonance imaging (MRI) [2]. Proof of direct viral invasion would need to be proven by a positive cerebrospinal fluid (CSF) polymerase chain

reaction (PCR) for SARS-CoV-2, intrathecal production of antibodies specific to SARS-CoV-2, or the presence of SARS-CoV-2 antigen or RNA in brain tissue taken during an autopsy or biopsy [1]. The presence of viral encephalitis should be evaluated in patients with COVID-19 who exhibit acute neurological signs such as seizures, confusion, headache, disorientation, epilepsy and altered mental status. Viral encephalitis confirmation requires PCR confirmation in the CSF. However, due to transient dissemination of SARS-CoV-2 virus and low CSF load, it becomes extremely difficult to confirm viral encephalitis in COVID-19. The negative PCR for SARS-CoV-2 virus in CSF and the lack of a characteristic CSF finding make the diagnosis of COVID-19 encephalitis less obvious [4–7].

We describe a probable case of SARS-CoV-2-associated encephalitis based on the World Health Organization (WHO) COVID-19 case definition [8].

Case presentation

A 62-year-old male with a medical history of arterial hypertension, obesity, and type 2 diabetes mellitus was admitted to the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia, complaining of high fever, fatigue, cough, and disturbed mental state. He was diagnosed with COVID-19, based on positive SARS-CoV-2 PCR test of a nasopharyngeal swab, 7 days before admission. He had fever up to 38 °C 7 days before admission and became disoriented and psychotic after 5 days. Chest X-ray was done upon admission to the hospital, and it revealed no abnormalities in lung parenchyma. In addition, CT scan of the head was done and it was normal. Meningeal signs were absent. The only focal neurological abnormality during hospitalization was ataxic gait. The results of laboratory analyses were normal, except slightly elevated D-dimer (1.39 mg/L), ferritin (478.2 μg/L), and white blood cells (WBC; 11.8×10^9/L). The chest CT scan did not reveal COVID-19 pneumonia and brain MRI revealed only cortical reductive brain alterations. Lumbar puncture was done on the day of hospital admission, and CSF was sent for biochemical analyses, culture, and meningitis-encephalitis panel PCR. CSF revealed 33 leucocytes per mm^3 (all were lymphocytes), glycorrhachia (8 mmol/L), and hyperproteinorachia (0.8 g/L) (Table 1). The meningitis-encephalitis panel PCR was negative, which excluded all possible viral or bacterial causes of encephalitis. The bacterial culture and SARS-CoV-2 PCR with CSF were negative (Table 1). The patient was diagnosed with viral encephalitis of unknown cause—most probably caused by COVID-19—due to the clinical picture and CSF laboratory findings (based on WHO COVID-19 case definition). Anti-edematous, anti-inflammatory, anticoagulant, gastroprotective, and other symptomatic medications were administered to the patient. He was not treated with antibacterial or antiviral therapy. The patient's condition improved in the next 10 days; and the control COVID-19 swab, after 10 days of hospitalization, was negative. The patient fully recovered and was released from the hospital with normal physical findings and without neurological abnormalities. In addition, his clinical findings were unremarkable during follow-up visits.

Discussion

The global pandemic caused by SARS-CoV-2 began in December 2019 and quickly spread throughout the world [9]. Although respiratory issues were previously thought to be the primary clinical symptoms of COVID-19, it was later discovered that COVID-19 can also cause damage to multiple organs [10–13]. Numerous mechanisms, such as virus-induced hyperinflammatory and hypercoagulable states, direct virus infection of the central nervous system (CNS), and postinfectious immune-mediated processes, could explain the neurological symptoms of SARS-CoV-2 infection [1].

The first research investigation of neurologic manifestations of COVID-19 from Wuhan, China, in which 214 hospitalized patients were reviewed, revealed that 36.4 % of patients showed neurological symptoms, and served as a basis for the evolution of the evidence regarding the neurological effects of COVID-

Table 1. Biochemical and microbiological findings of cerebrospinal fluid analysis of the patient with COVID-19 encephalitis.

Cerebrospinal fluid	Values
White blood cell count (mm^3)	33
Mononuclear leukocytes (%)	33
Polymorphonuclear leukocytes (%)	0
Glucose (mmol/L) *	8
Protein (g/L)	0.8
Gram stain	Negative
SARS-CoV-2 PCR	Negative
Multiplex PCR meningitis-encephalitis panel **	Negative
Enteroviruses (ELISA)	Negative
West Nile virus (ELISA)	Negative
Tick borne encephalitis virus (ELISA)	Negative
Borrelia burgdorferi (ELISA)	Negative

* Glycemia 15.3 mmol/L. ** *Escherichia coli* K1, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Cryptococcus neoformans/gattii*, varicella zoster virus (VZV), herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV- 6), human parechovirus, cytomegalovirus (CMV), enterovirus. COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ELISA: enzyme-linked immunosorbent assay.

19 [14]. Self-reported symptoms such anosmia and dysgeusia, neuropathic pain, myalgia, and vertigo are some of the different neurological characteristics. Acute encephalopathy, acute hemorrhagic necrotizing encephalopathy, meningitis, encephalitis, myelitis, and myopathies are among the neurological syndromes that have been recorded. Miller Fisher syndrome, polyneuritis cranialis, and Guillain-Barre disease, all showed signs of PNS involvement. Numerous investigations revealed a comparable array of neurological presentations, including cerebral venous thrombosis, mono/polyneuropathies, acute disseminated encephalomyelitis, and encephalitis [15–22]. A multi-center retrospective research study by the Spanish Society of Neurology found that 2.2% of COVID-19 patients with neurological signs had encephalitis, indicating a low frequency among hospitalized SARS-CoV-2 patients [23]. Siow *et al*. noted that encephalitis ranks second in terms of neurological complications, after stroke [24]. The average incidence of encephalitis reported as a COVID-19 complication was 0.215%, which is not statistically different from the findings of other authors [25,26]. In February 2020, a male 24-year-old patient with acute febrile confusion, and a generalized tonic-clonic seizure was proven to be the first instance of COVID-19-associated meningoencephalitis [7].

The majority of patients with SARS-CoV-2-linked CNS inflammation showed negative SARS-CoV-2 CSF PCR, despite the fact that an increasing number of cases of SARS-CoV-2-associated encephalitis have been documented. Many of these cases do not meet the rigorous criteria for the diagnosis of SARS-CoV-2-associated encephalitis [5,25,27–30]. Since the virus was not detected in CSF in many reported cases, despite evidence of inflammation, as demonstrated by CSF pleocytosis and elevated protein; it raised the possibility that some cases of COVID-19 encephalitis may occur in the absence of direct viral invasion and potentially result from immune-mediated inflammatory mechanisms [1]. False negative results can be caused by a brief period of viremia, a small number of SARS-CoV-2 particles at quantities below the test method's limit of detection, or a delay in testing CSF for SARS-CoV-2 after symptoms were observed [24]. Additionally, it is thought that the virus is primarily cell-bound and spreads from one cell to another. Low amounts of proteins and endonucleases/exonucleases may potentially have an inhibitory effect on CSF. Additional plausible explanations for the pathophysiology of encephalitis as a consequence of COVID-19 include the SARS-CoV-2 virus-induced systemic inflammation, the innate immune system's activation through the release of copious amounts of inflammatory cytokines (interferon/IFN-α, IFN-γ, IL-1β, IL-6, and IL-12), and a molecular mimicry mechanism [25,31–33]. The majority of patients experienced SARS-CoV-2 infection signs approximately 7 days prior to the start of neurological symptoms.

The most commonly reported symptoms of SARS-CoV-2-associated encephalitis were changed mental state, headaches, seizures, and consciousness disruption [24,34,35]. Increased protein and lymphocytic pleocytosis were found in the CSF of the majority of SARS-CoV-2 encephalitis cases [1,5,24,27,34,36–38]. Laboratory findings included elevated ferritin, D-dimer, C-reactive protein (CRP), WBC count, and other inflammatory markers [34,37,38].

Infection or inflammation in SARS-CoV-2-associated encephalitis can affect any area of the brain, but it is more common in the temporal lobe, white matter, frontal lobe, and corpus callosum. The brain CT scan is usually unremarkable. Hemorrhagic lesions on T2/FLAIR sequences and diffuse white matter hyperintensities are common MRI brain findings [39–41]. Additionally, a large number of COVID-19 patients do not exhibit notable encephalitis-related neuroimaging abnormalities. Diffuse slow waves are the predominant EEG expression in most patients with SARS-CoV-2-associated encephalitis; however, few individuals also show focal epileptic waves or generalized delta activity [1,2,5,26,27,36,37]. While certain imaging results are linked to the neurotropism of COVID-19; others are linked to different reasons, including coagulopathy, hypoxia, cytokine storm syndrome, subclinical seizures, and encephalopathy associated with critical illness [42,43]. Meppiel *et al.* [35] conducted multi-center research in which they found that 22 (9.5%) individuals with neurological symptoms linked to SARS-CoV-2 infection had encephalitis. Every patient had a changed mental state, and focal neurologic deficiency was present in 57.1% of the cases. A CSF analysis usually reveals lymphocytic pleocytosis. However, in 66.7% of patients, the brain MRI revealed abnormalities, and these neuroimaging findings were inconsistent. CSF samples of only two patients had a positive SARS-CoV-2 PCR result.

The absence of Toscana virus testing is a limitation of our study; although this case did not occur during the warm period of the year which is typical for the virus.

Conclusions

The diagnosis of SARS-CoV-2 encephalitis can be challenging, and is usually based on the exclusion of other etiological agents of brain infections. Even though encephalitis is a rare manifestation of COVID-19, immunocompromised patients have a higher possibility of developing encephalitis caused by SARS-CoV-2.

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Conflict of interests

No conflict of interests is declared.

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