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Case report

SARS-CoV-2-associated first episode of acute mania with psychotic features

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ABSTRACT

Despite neuropsychiatric outcomes of SARS-CoV-2 infection are now under close scrutiny, psychoneuroimmunological characteristics of COVID-19 and precise pathophysiology of neuropsychiatric manifestations of the infection are still obscure. Moreover, there still exists a shortfall in demonstrating specific clinical manifestations of the brain involvement of the virus. Here, we presented a 33-year-old female patient with COVID-19, reporting acute-onset paranoid delusions symptoms, insomnia and irritability. Cranial MRI showed an hyperintense signal in the splenium of the corpus callosum with decreased apparent diffusion coefficient, which might possibly indicate the presence of cytotoxic edema related to the brain involvement of the infection. Following the completion of SARS-CoV-2 treatment, both cytotoxic edema and psychiatric symptoms resolved. In light of this report, we suggest that either heightened immune response and direct viral infection that SARS-CoV-2 may lead to such psychiatric manifestations and neuropsychiatric monitoring should be performed in patients with COVID-19. Prompt recognition of psychiatric consequences of COVID-19 may help clinicians provide guidance for differential diagnosis and manage them accordingly.

1. Introduction

With the worldwide spread of Coronavirus Disease-2019 (COVID-19), which is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), neuropsychiatric outcomes of the disease are now under close scrutiny, although the virus mainly targets the respiratory tract. The precise pathophysiology of neuropsychiatric manifestations of the infection is still obscure; nonetheless, it has been suggested that either SARS-CoV-2 may infiltrate into central nervous system (CNS) directly or it may induce neuroinflammation as a result of its immunoreactivity [1,2]. Although a substantial body of literature has been published regarding the possible neuropsychiatric aspects of SARS-CoV-2 infection [3,4], there still exists a shortfall in demonstrating clinical manifestations of the CNS involvement of SARS-CoV-2. Here, we present a patient with COVID-19, reporting psychotic symptoms, insomnia and irritability which may be suggestive of a psychiatric manifestation of the infection.

2. Case report

A 33-year-old high-school-graduated female patient was admitted to our psychiatric emergency unit with the complaints of irritability and decreased need for sleep for the last 2 days. She was noticed to have strongly held but irrational beliefs that her children were under the effect of bad spirits and that they were in danger. The patient's family members reported an irrational anger of the patient towards her husband with the false belief that he was having an extra-marital affair. The patient had no previous background of neurological nor psychiatric diagnosis and no prior alcohol or substance abuse. Findings of the mental state examination were as follows: cooperation and orientation were intact, speech output and speed, as well as psychomotor activity were increased. The patient was anxious, while her mood was dysphoric. Derailment, persecutory, mystic and infidelity delusions with no insight were recorded. Scores from the Positive and Negative Syndrome Scale (PANSS) and Young Mania Rating Scale (YMRS) were 89 and 43, respectively. The patient's physical examination revealed sore throat and fever with a temperature of 37.8 °C. Her neurological examination was non-significant. The patient was hospitalized, and her treatment was started with haloperidol 20 mg/day and biperiden 10 mg/day i.m. with the initial diagnosis of acute manic episode of bipolar disorder. Blood tests and mag-

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netic resonance imaging (MRI) of brain were performed to exclude any medical conditions. Cranial MRI showed an hyperintense signal in the splenium of the corpus callosum with decreased apparent diffusion coefficient, which might possibly indicate the presence of cytotoxic edema (Fig. 1a). Blood screening results at admission showed increased levels of white blood cell count (9.62 Lx 10^3/μL), C-reactive protein (CRP) (123 mg/dL), fibrinogen (625 mg/dL), ferritin (214 μg/L) and D-Dimer (1.25 μg/mL), while thyroid, liver and renal functions, creatine kinase (CK), and electrolytes were in the normal range. Since the clinical symptoms and laboratory values indicated high levels of CRP, D-dimer, fibrinogen and ferritin, COVID-19 was suspected. Computerized tomography (CT) of the chest and the real time - polymerase chain reaction (RT-PCR) test for SARS-CoV-2 were performed using a nasopharyngeal swab. Although the RT-PCR test was negative for SARS-CoV-2 infection, SARS-CoV-2 antibody test conducted via blood work detected IgM antibodies. Besides, the patient's CT scan of the chest showed bilateral ground-glass opacities which were consistent with SARS-CoV-2 infection (Fig. 1b). Hydroxychloroquine at 400 mg/day and favipiravir at 1200 mg/day, which was the current national protocol for the treatment of COVID-19, was administered to the patient per oral. In addition, her psychiatric treatment was switched to olanzapine at 20 mg /day. A follow-up MRI of the brain at the fifth day of the treatment showed complete resolution of cytotoxic edema in the corpus callosum while a follow-up blood screening at the tenth day of the treatment showed significant improvements in CRP (21 mg/dL), fibrinogen (400 mg/dL), ferritin (110 μg/L) and D-Dimer (0.7 μg/mL). The PANSS and YMRS scores at the fourteenth day of the treatment were 47 and 19, respectively. After completion of treatment, the patient was discharged with olanzapine at 20 mg/day per oral.

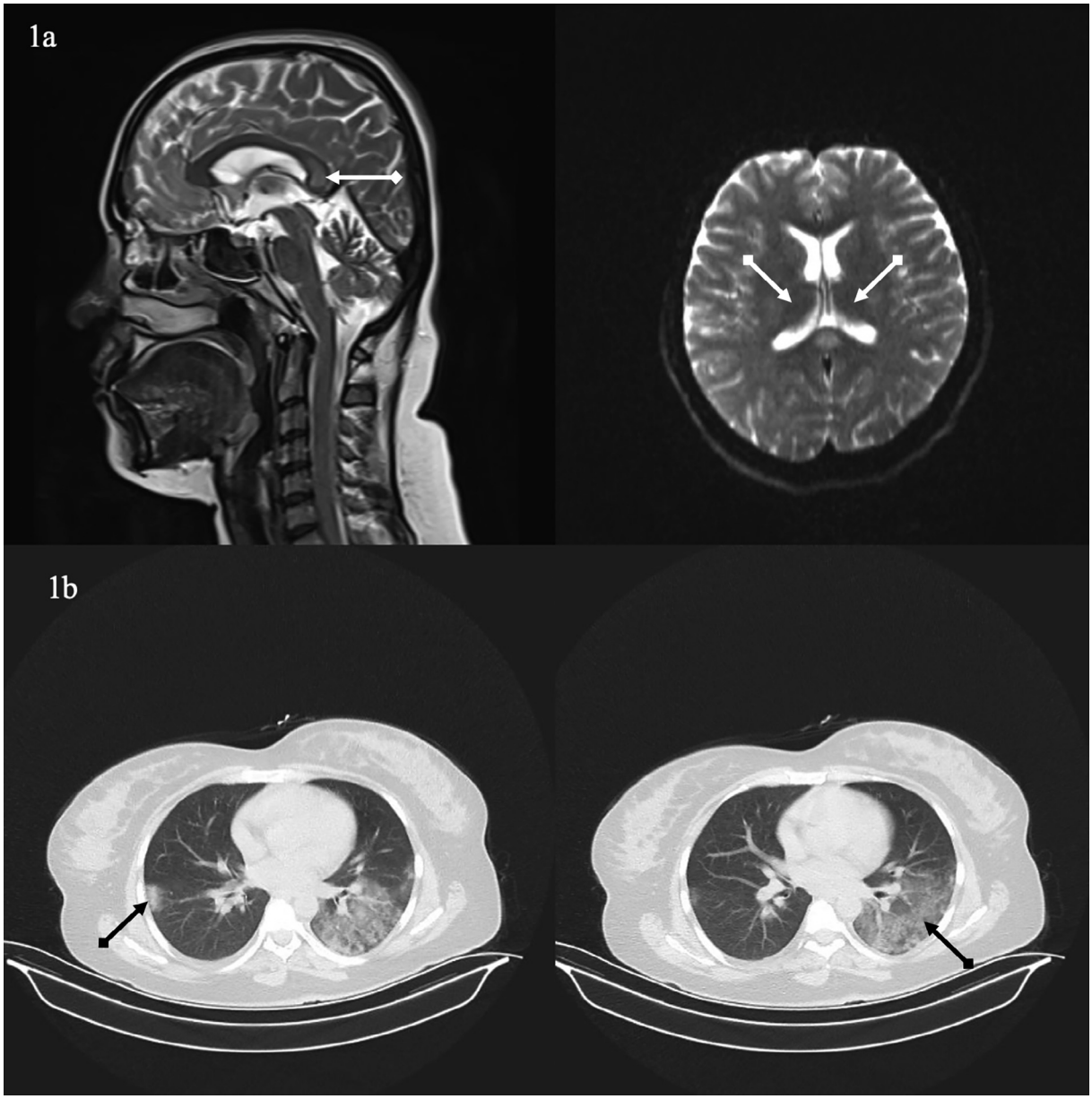

Fig. 1. a: MRI of the brain showed hyperintense signal in the splenium of the corpus callosum with decreased apparent diffusion coefficient, which possibly indicates the presence of cytotoxic edema on brain MRI, 1b: CT scan of the chest showed bilateral ground-glass opacities.

3. Discussion

This letter reports a case of COVID-19-associated manic symptoms including irritability and disorganized behaviors with psychotic features in a female patient. Neuropsychiatric complications such as affective psychosis after COVID-19 infection [5] and psychotic episode as a *coronaphobic reaction* have been recently reported [6]; however, to the best of our knowledge, this is the first report of a patient who developed both acute affective and psychotic symptoms associated with corpus callosum cytotoxicity as a consequence of COVID-19 infection. In addition, the absence of exogenous corticosteroid use, which is known to cause affective-psychotic symptoms [7] and is frequently used in the management of COVID-19, is an important fact that supports our hypothesis that the neuropsychiatric manifestation in our patient is directly related to the infection itself. Infection with SARS-CoV-2 may cause a wide variety of symptoms with neuropsychiatric implications even though the virus mainly aims to the respiratory system. It has been suggested that SARS-CoV-2 may transmit to the CNS via retrograde axonal transport from the olfactory nerve and invade neurons directly following colonization in the respiratory tract [8,9]. In addition to its direct neuroinvasive potential, the virus may bind to angiotensin converting enzyme-2 (ACE-2) receptors expressed in glia and neurons, which may trigger an inflammatory response by increasing cytokine release in the CNS. Similarly, in peripheral cells, SARS-CoV-2 may bind to and infect the peripheral immune cells and this may lead to an acute immune response with the excessive production and release of proinflammatory chemokines and cytokines particularly TNF-α, IL-1 and IL-6 [1,2]. This aggressive antiviral immunoreactivity in COVID-19 is often referred to as the *cytokine storm*. Reactive oxygen species generated due to the stimulation of cells by the cytokine storm may cause collateral damage to various organs. Neurodegeneration can also be an outcome from the penetration of peripheral cytokines into the CNS via a blood–brain-barrier made dysfunctional from increased levels of inflammatory components.

The splenium of the corpus callosum is known to be vulnerable to cytotoxicity [10] and lesions in the splenium, particularly in the anterior region, have been reported to be associated with psychiatric symptoms including insomnia, irritability, behavioral changes and psychosis [11]. Viral infections including influenza, adenovirus and rotavirus may be causative factors for corpus callosum damage [10]. In light of the current knowledge, in our patient, SARS-CoV-2 infection may have resulted in damage to the corpus callosum directly or indirectly via the cytokine storm.

COVID-19 has been suggested to play a role in not only bringing forth several psychiatric manifestations but also in triggering the recurrence of pre-existing psychiatric conditions, although more studies are needed to confirm such an argument. Neurodegenerative process may be caused by the virus directly or may be triggered by the excessive antiviral immune response following the infection. Prompt recognition of psychiatric consequences of COVID-19 may help clinicians provide guidance for differential diagnosis and manage them accordingly.

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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