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Case Report

Lethal encephalitis in a pediatric patient with SARS-CoV-2

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ABSTRACT

Background. SARS-CoV-2 mostly affects the respiratory system. Some studies have reported neurological disorders associated with SARS-CoV-2. Despite an increase in reported instances, encephalitis caused by COVID-19 infection is still poorly understood.

Case. We reported a rare presentation of SARS-CoV-2 in a 15-year-old patient. He had a fulminant course with encephalitis. He had mild symptoms of a COVID-19 infection five months ago and recovered without any sequel. Despite appropriate treatment, the patient had a devastating course.

Conclusions. This was a severe presentation of SARS-CoV-2 with central nervous system manifestations.

Key words: encephalitis, status epilepticus, SARS-CoV-2, childhood.

Encephalitis is an inflammation-related neurological illness affecting the brain parenchyma.

It is characterized by focal brain changes, with or without meningeal involvement, and can be caused by a variety of factors (infectious, inflammatory, autoimmune, paraneoplastic, etc).[1-3] Viral encephalitis is the most common infectious cause of encephalitis. It presents with fever, headache, clouding of consciousness, seizures, personality change, focal neurologic deficits, coma, and death.[1,2]

SARS-CoV-2 manifests as fever, cough, fatigue, and pneumonia. Studies have shown that SARS-CoV-2 can cause central nervous system manifestations such as seizures, altered levels of consciousness, cerebral ischemia, and encephalitis.[4]

Patients with SARS-CoV-2 encephalitis may have mild respiratory symptoms at the beginning; later on clinical findings may progress to deterioration and loss of consciousness progressing to confusion.[5] Here we represent a pediatric case of SARS-CoV-2 encephalitis with a devastating course.

Case Report

A 15-year-old male patient was admitted to an outpatient emergency clinic at a local hospital. He had a headache, sore throat, loss of appetite, malaise, and vomiting for one week. He had a history of a COVID-19 infection five months ago. Three days before admission, he had vertigo, clumsiness, and drop attacks. He had used antihistamine without a prescription. Afterwards, he had a tendency to sleep. The physician who had examined him had attributed this sleep event to the antihistamine drug. Brain computed tomography (CT) revealed normal findings. On the seventh day of initial symptoms, his parents took him to the hospital when they could not awaken him. The patient's consciousness ameliorated. He was hospitalized at the local hospital. On the first morning of admission at the local hospital, he became comatose with a Glasgow coma scale (GCS) of 3, he was intubated and referred to our hospital. Physical examination on admission

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was as follows: temperature: 39°C, blood pressure: 110/70 mmHg, pulse rate: 90 bpm, and respiratory rate: 20 bpm; he had a GCS of 3, no lateralization, or neck stiffness. He had an extensor plantar response. His laboratory findings were normal. On the third day of admission, D dimer (1.14 mg/L), Troponin I (150 pg/ml), and BNP (38.2 pg/ml) increased.

Blood culture and sputum culture revealed no organism. A thorax CT revealed bilateral infiltrations in the lower segments, as well as subpleural atelectasis in the posterior lower segment of the left lung. Brain CT was normal, and brain magnetic resonance imaging (MRI) did not reveal any abnormality in axial brain MRI images T1W, T2W, FLAIR, or post contrast T1W images, but there was significant diffusion restriction at frontotemporoparietal cortical areas bilaterally representing cytotoxic edema in diffusion-weighted images (DWI) (Fig. 1).

In the light of his physical examination, clinical findings, and brain MRI findings, the patient was considered to have encephalitis. Other infectious agents could not be ruled out due to laboratory insufficiencies. The lumbar puncture could not be done because the GCS was 3 and the parents did not provide informed consent. Vancomycin, ceftriaxone, favipiravir, and acyclovir treatment were initiated. Because of the severe involvement of the central nervous system and GCS of 3 on admission, daily intravenous immunoglobulin (1 gram/kg/day IVIG for 2 days) was added to his regimen. The patient developed status epilepticus within 6 hours of admission after the first dose of IVIG. We obtained a non-enhanced CT, which revealed cortical sulci effacement, representing brain edema (Fig. 1). Mannitol, dexamethasone, and 3% NaCl were added to the patient's treatment. We started plasmapheresis and discontinued after the third session due to hypotension. The patient deteriorated despite treatment. He had non-reactive pupils in the midline, an absent gag reflex, oculovestibular, oculocephalic, and cornea reflexes, showing that he was brain dead 48 hours after admission. Carotids Doppler ultrasonography (USG) revealed disruption of both internal carotid artery (ICA) and middle cerebral artery (MCA) arterial flow forms with a pattern of high- resistance short-duration reverse flow. The patient died on the eighth day of admission.

Discussion

SARS-CoV-2 has potential neurovirulence and can cause neurological disorders in a short or long-term span due to inadequate immune responses and/or viral propagation in the central nervous system (CNS).[6,7] Neurological complications vary from mild to severe such as headache, anosmia, disturbance of consciousness, seizures, and paralysis. Neurological symptoms can follow respiratory symptoms with a delay.[8] In a recent study from France, 58 of 64 COVID-19 patients had neurologic problems, including encephalopathy, agitation, and confusion.[9] The pathophysiology of SARS-CoV-2-associated encephalitis is not completely known. The pathogenesis of encephalitis as a COVID-19 consequence has been proposed in three ways: molecular mimicry, direct invasion of the neurological system, and systemic inflammation.[10-13] Numerous penetration routes have been proposed, including the hematogenous route and trans-synaptic transmission. Disruption of the blood-brain barrier (BBB) may be a hallmark of SARS-CoV-2 neuropathogenesis. By regulating the entry of immune cells or viruses into the CNS, the BBB plays an important role in the pathogenesis of neurotropic viruses. By interacting with angiotensin converting enzyme-2 (ACE-2) on neurons and glia, the virus might start a cycle of viral budding and further harm neuronal tissue once it has access to it.[14] On the other hand, if the innate immune system fails to cope with SARS-CoV-2, the adaptive immune system, which is systemic, and virus-specific, will be activated, resulting in immunological memory stimulation. Cell-mediated immunity and humoral immunity are frequently part of the adaptive immune response. Nonetheless, if a virus escapes the immune system and causes

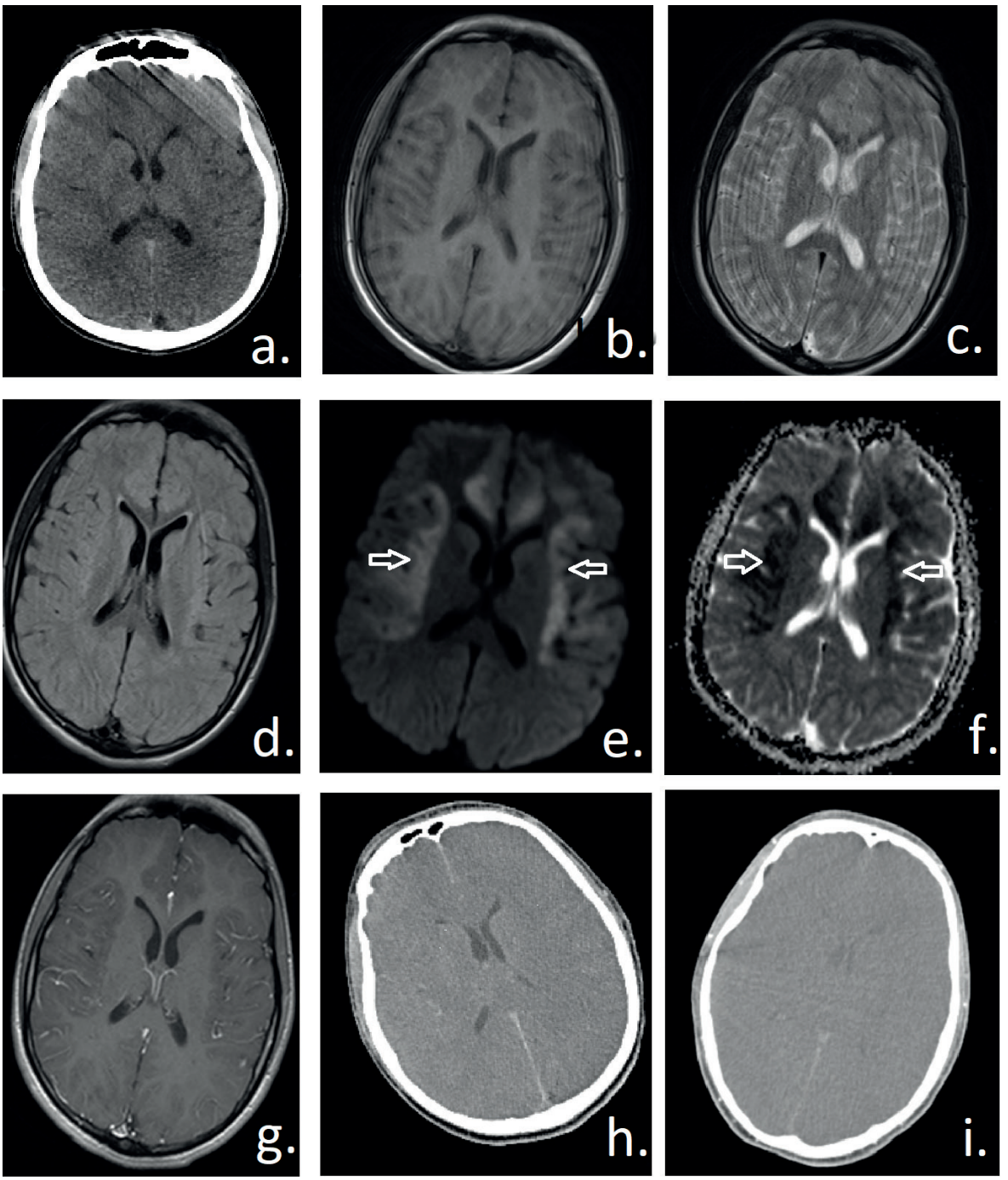

Fig. 1. Radiologic features with severe brain involvement.

Axial non-enhanced brain CT (a), axial brain MR images T1W (b), T2W (c), FLAIR (d), post contrast T1W (g) images show no significant abnormality. In diffusion-weighted images (e) and ADC (f), significant diffusion restriction is seen in frontotemporoparietal cortical areas bilaterally (arrows), representing cytotoxic edema. 16 hours later, a second axial non-enhanced brain CT (h) was obtained and cortical sulci effacement was seen, representing brain edema. A third post-contrast brain CT (i) was obtained 14 hours after the second brain CT and significant brain edema with loss of brain perfusion is seen.

enhanced viral replication or over reactive innate immune responses, viral infections can spread to all CNS regions. Following the activation of glial cells by SARS-CoV-2 viruses, various inflammatory chemokines and cytokines are produced. Increased inflammatory infiltrates can exacerbate neuroinflammation and cause neuronal damage.[14] Molecular mimicry is a third proposed mechanism for encephalitis as a COVID-19 complication.[10] The increase in the host antibodies and lymphocytes occurs in response to infection with the SARS-CoV-2 virus. Although these immune molecules are expected to be specific for antigens of the SARS-CoV-2 virus, some of them are cross-reactive and attack self-antigens.[10] Although virus isolation is essential for a definite diagnosis of viral encephalitis, it is problematic with COVID-19 because SARS-CoV-2 transmission is transitory and the CSF titer may be exceedingly low and it may not be positive in some circumstances.[5,7] The neurological symptoms are seen in severely affected patients.[15] Our patient did not have severe respiratory symptoms at the beginning; he had neurological symptoms with dizziness, headache, and finally loss of consciousness. He had normal laboratory values except for the positive viral PCR. Rapid deterioration might be due to the former SARS-CoV-2 which he had five months ago. The adaptive immune system might be activated, resulting in immunological memory stimulation and resulted in extensive damage in the CNS.

Imaging in viral encephalitis shows focal or diffuse altered cerebral signal intensity, cerebral edema, diffusion restriction, hemorrhages, necrosis, and enhancement.[16] With the invasion of viruses, signal changes in DWI are divided into the acute stage, which constitutes congestion, perivascular cell infiltration, and thrombus formation; late acute and early subacute stages that constitute vasculitis. Perivascular cell infiltration decreases, leading to a decrease in the severity of diffusion restriction at this stage.[17] We had detected significant diffusion restriction at the frontotemporoparietal cortical areas bilaterally representing cytotoxic edema in diffusion-weighted images supporting acute encephalitis. Our patient did not have a relapsing-remitting or progressive course of neurologic symptoms after the first COVID-19 infection. He had an acute onset of neurologic symptoms when he was re-infected. Our patient's symptoms were devastating within seven days. We accept neurological involvement as a para-infectious phenomenon with acute symptoms and MRI findings.

Treatment of SARS-CoV-2 is largely supportive.[5] COVID-19 related inflammatory CNS diseases such as encephalitis were successfully treated with a combination of intravenous immunoglobulin and corticosteroids, of these patients 11 of the 12 had recovered.[18] Plasmapheresis was also demonstrated to be beneficial in a case series of six severely ill COVID-19 encephalitis, with five of them recovering enough to be discharged from the ICU to a regular ward after plasmapheresis.[19] We preferred IVIG and plasmapheresis. We did not add high dose corticosteroids to the treatment because we could not rule out any other infective causative agents.

SARS-CoV-2 can invade the nervous system. Encephalitis may be devastating. Brain MRI may show early findings in the diffusion-weighted series. The other series of MRIs may be normal. We recommend MRI with diffusion-weighted images early in the neurologic disturbance to rule out lesions causing cytotoxic edema. Despite proper timing of antiviral and other supportive treatments for CNS involvement, the clinical outcome may be poor. More cases are needed to understand the neurologic involvement with SARS-CoV-2.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SY; data collection: KZ; analysis and interpretation of results: SY, AMA, ATY; draft manuscript preparation: SY. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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