Brief Report

A Toddler With Acute Encephalitis Associated With COVID-19: A Case Report

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Background

December of 2019 was marked the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease 2019 (COVID-19) pandemic. It spreads from person to person, usually through close respiratory droplets affecting mainly the respiratory system.[1] This disease can cause a broad spectrum of clinical manifestations, ranging from mild to severe and critical, eventually leading to death.[2] Although some neurologic manifestations such as acute cerebrovascular disease, ischemic and hemorrhagic strokes, and skeletal muscle injuries have been reported in some adults with COVID-19,[3-5] encephalopathy is a rare condition caused by SARS-CoV-2 infection. Overall, the incidence and severity of the disease have been relatively mild in children with a lower fatality rate compared with adults.[6] However, in this article, we report a toddler who passed away because of acute encephalitis associated with COVID-19.

Case Presentation

The patient was a 1-year-old boy, the only child of consanguineous parents (cousins) who had lost their first child (daughter) from a flu infection at the age of 6 years. The patient was presented to the emergency department of Tabriz Children Hospital with fever (39.2 °C) and 2 episodes of generalized tonic-clonic seizures. He had received the measles, mumps, and rubella (MMR) vaccine 12 days before the admission. The child was lethargic. His pupils were midsized and reactive to light, with no papillary edema. He had 2+ deep tendon reflexes bilaterally in the upper and lower extremities, with downgoing toes. He also had tachycardia due to fever. Auscultation of the lungs was normal. The abdominal examination was normal without tenderness or organomegaly. The patient underwent a lumbar puncture due to concern for meningoencephalitis or post-MMR vaccination aseptic meningitis. The appearance of the cerebrospinal fluid (CSF) sample was clear. No white blood cells or red blood cells were seen. Protein and glucose levels were 108 mg/dL and 72 mg/dL (serum glucose 113 mg/dL), respectively. The Gram stain of his CSF showed no cells or organisms that ruled out bacterial meningitis. The patient subsequently underwent a brain computed tomography scan, which revealed diffuse hypodensities involving the corpus callosum with a predominance in the splenium, peritrigonal white matter on both sides, and the left thalami. Therefore, encephalitis, and acute disseminated encephalomyelitis were considered as the possible differential diagnosis. As the pulse therapy, methylprednisolone and intravenous acyclovir were administered; however, no improvement occurred in the level of consciousness. A brain magnetic resonance imaging (MRI) was subsequently performed to differentiate these conditions. Abnormal T2/fluid-attenuated inversion-recovery (FLAIR) hyperintense lesions were noted, particularly in the entire corpus callosum, ventral aspect of medulla oblongata, and cerebellar vermis. Hyperintense lesions on axial T2-weighted image were also noted in the bilateral thalami, corpus callosum, bilateral peritrigonal white matter, and cerebral cortex. Restricted diffusion in corpus callosum and periventricular white matter, as well as bilateral subdural effusion were demonstrated on diffusion-weighted imaging and apparent diffusion coefficient mapping. Acute progressive encephalitis was eventually reported in the brain MRI (Figure 1). Intravenous immunoglobulin was administered after getting the brain MRI results for autoimmune encephalitis possibility on the first day of admission. However, there was still no change in the level of consciousness. On the second day of admission, due to the COVID-19 pandemic situation, blood and nasopharyngeal swab samples were obtained from the patient for serological and molecular detection of

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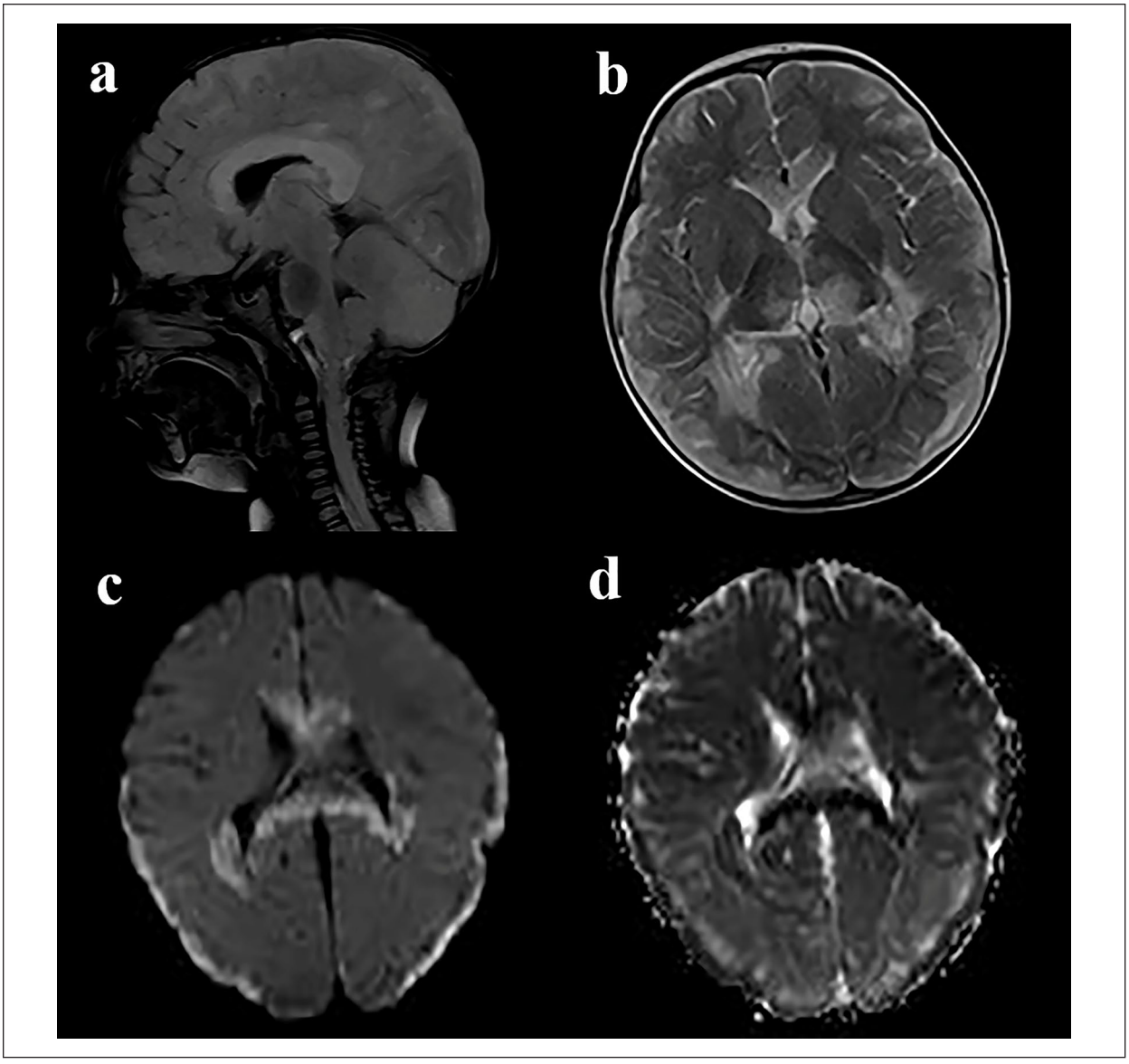

Figure 1. Magnetic resonance imaging of the reported patient with acute progressive encephalitis associated with coronavirus disease 2019. Abnormal T2/fluid-attenuated inversion-recovery hyperintense lesions are noted in the entire corpus callosum, ventral aspect of medulla oblongata, and cerebellar vermis (a). Hyperintense lesions on axial T2-weighted image are noted in bilateral thalami, corpus callosum, bilateral peritrigonal white matter, and cerebral cortex (b). Restricted diffusion in the corpus callosum and periventricular white matter, as well as bilateral subdural effusion, are seen on diffusion-weighted imaging (c), and apparent diffusion coefficient mapping (d).

COVID-19, respectively. Although the reverse transcription real-time polymerase chain reaction (rRT-PCR) test from the nasopharyngeal swab result became negative, anti-SARS-CoV-2 immunoglobulin G and immunoglobulin M both were positive in enzyme-linked immunosorbent assay. Since the patient was hospitalized with the possibility of aseptic meningitis caused by the MMR vaccine, the taken CSF sample was not tested for COVID-19 or other possible viral infections on the first day of hospitalization. On the third day of hospitalization, the child developed respiratory distress requiring mechanical ventilation and was transferred to the pediatric intensive care unit for further management. According to the patient's unstable condition and intubation, it was impossible to re-perform lumbar puncture and test COVID-19 on the CSF sample in the following days. During the third to 13th days of hospitalization in the intensive care unit, he gradually developed multiorgan damage. The patient developed electrolyte disturbances and elevated serum urea, creatinine, and liver

enzymes alanine and aspartate aminotransferases. The electrolyte balance of the patient was checked and corrected as needed. Despite the withdrawal of all sedative drugs, the patient's level of consciousness did not improve. Pupillary light responses, as well as oculocephalic and oculovestibular reflexes, were absent. Electrolyte disturbances, metabolic disorders, and hypothermia gradually improved. However, there were still signs of brain death due to a negative apnea test on the 13th day of hospitalization. On the 14th day, the atropine and apnea tests were still negative, and unfortunately, the patient passed away.

Discussion

Pediatric COVID-19 has been reported to have a milder presentation, fewer complications, and a lower fatality rate than the disease in adults.[6] Our report presents a toddler with a severe neurologic involvement (encephalitis) possibly associated with COVID-19 infection. Several viruses can invade the central nervous system (CNS) and infect resident cells, including neurons.[7] Some reports have revealed the association of human coronaviruses with neuronal involvement.[3-5] Bhavsar et al[8] reported a 16-year-old previously healthy male with acute encephalitis associated with COVID-19. A case was also reported by Yeh et al[9] in which human coronavirus-OC43 was detected in the CSF of a 15-year-old male presumed to have acute disseminated encephalomyelitis. Acute encephalitis is a rare condition resulting from possible CNS inflammation caused by SARS-CoV2-2.[8] Inflammation of CNS can be due to multisystem inflammatory syndrome in children (MIS-C). This syndrome that shares characteristics of Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome, has been described in the United Kingdom, France, Italy, and the United States, among other countries.[6,10] It now is considered as a significant medical risk in children with COVID-19.[11] In the present case, acute encephalitis was eventually reported as the brain MRI result demonstrating the possibility of neurologic involvement caused by SARS-CoV-2. Although the COVID-19 rRT-PCR test result was negative, the positive antibody test result could indicate an earlier infection in this patient that might gradually lead to multi-organ damage, CNS inflammation, and encephalitis possibly associated with MIS-C. Based on recent studies, neurological involvement may be frequent in MIS-C patients. However, this syndrome confers a challenge for pediatricians due to its variable clinical presentation such as neurologic involvement, gastrointestinal symptoms, cardiac disease, respiratory symptoms, laboratory evidence of inflammation, and variable incidence of fever, rash, red eyes, and oral mucous membrane changes. MIS-C can present at any time, but it usually occurs from 1 to 6 weeks following infection. It may also overlap with the COVID-19 presentation.[12,13]

Agarwal et al[14] reported a pattern termed virus-associated acute necrotizing disseminated leukoencephalopathy in 8 patients presented with white matter cytotoxic lesions and brain atrophy associated with COVID-19. Gaughan et al[15] reported a 16-year-old girl with a confirmed COVID-19 infection who suffered from visual hallucinations and ritualistic behaviors. She presented several clinical features of akinetic mutism, such as lack of voluntary spontaneous movements, absence of speech, and preserved visual tracking. de Miranda Henriques-Souza et al[16] reported a 12-year-old girl with confirmed COVID-19 presented with a skin rash, headache, and fever. The neuroimaging hallmarks were diffuse subcortical and deep white matter–restricted diffusion, focal T2/FLAIR hyperintense lesions in the corpus callosum's splenium, inferior medulla, and extensive cervical myelopathy. These features favored the diagnosis of acute disseminated encephalomyelitis following the SARS-CoV-2 infection. Direct and indirect CNS lesions caused by SARS-CoV-2 might be possibly due to a parainfectious immune-mediated disease and activation of an autoimmune response against the CNS caused by the SARS-CoV-2 infection.[16,17]

Although rRT-PCR is still considered the gold standard test for diagnosing COVID-19, the test has also a false-negative rate. Some parameters including disease stage, clinical condition, sample type, quality of sample collection, transfer and storage qualities of samples, accuracy of PCR steps, laboratory errors, type of target gene, and possible mutations of SARS-CoV-2 genome can affect the sensitivity of the rRT-PCR, possibly resulting in a false result.[1] Morfopoulou et al[18] reported an 11-month-old boy with severe combined immunodeficiency, who had signs of viral encephalitis. His initial conventional diagnostic PCR test result was negative. After getting written informed consent from his family, a brain biopsy sample was obtained in their study, 2 months after the onset of the symptoms. RNA sequencing was done, which showed the presence of human coronavirus-OC43. It was then confirmed by rRT-PCR and brain immunohistochemical analysis. Deep sequencing of biopsy samples can provide a helpful diagnostic approach for unexplained encephalopathies.[18] However, in the present case, a brain biopsy was not obtained due to ethical concerns, which could be considered a study limitation. As other limitations, although the course of methylprednisolone and intravenous immunoglobulin was completed for autoimmune encephalitis possibility, the taken CSF sample on the first day of admission was not tested for autoimmune encephalitis. It was also tricky to re-perform lumbar

puncture and test COVID-19 or other possible viral infections on the CSF sample in the following days due to the patient's unstable condition and intubation.

It can be concluded that acute encephalitis can be caused by SARS-CoV-2 even in toddlers. It is imperative that patients with symptoms compatible with COVID-19 and encephalitis be tested for SARS-CoV-2 as well as other usual pathogens associated with neurological manifestations. A broad initial plan with a multi-disciplinary team may be necessary for children who meet the reported case presentation to successful outcomes.

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Author Contributions

BP: Contributed to conception; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
SR: Contributed to conception; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MB: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

Bita Poorshiri and Sina Raeisi are equally contributed as co-first authors. The author(s) declared no other potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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