Acute Necrotizing Encephalopathy Associated with SARS-CoV-2 Infection in Children

Dear Editor,

Acute necrotizing encephalopathy (ANE) is a rare neuroinflammatory condition characterized by the presence of multiple necrotic lesions that are symmetrically distributed. It is predominantly observed in children and is associated with a poor prognosis. Although ANE has been reported in adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) infection, it is rarely observed in children.[1] Herein, we report on the serum cytokine analysis of a rare case of ANE caused by SARS-CoV-2 infection in a Chinese girl.

A previously healthy girl aged 3 years and 11 months presented to the emergency room with a fever reaching up to 41°C for 2 days, accompanied by vomiting and increasing lethargy. Upon neurologic examination, she displayed reduced consciousness (Glasgow Coma Scale score of 9: E3V2M4) with no signs of meningeal irritation abnormalities. The girl also exhibited dysarthria, characterized by slow, slurred speech

and a low pitch of voice. Her modified Rankin Scale (mRS) score was 4. SARS-CoV-2 infection was confirmed through nasopharyngeal polymerase chain reaction (PCR) swab, and subsequent tests on day 2 and day 4 of hospital admission also yielded positive results for SARS-CoV-2 PCR. Her father, mother, grandfather, and grandmother previously experienced cough and high fever, and they too tested positive for SARS-CoV-2 RNA five days before the girl's illness onset. Lumbar puncture showed a slightly elevated protein level (0.55 g/L, normal range: 0.15–0.45 g/L) in the cerebrospinal fluid (CSF), with normal red and white cell counts, glucose, chloride, and lactic dehydrogenase (LDH) levels. PCR-based testing of CSF revealed SARS-CoV-2 RNA, herpes simplex virus 1 and 2, varicella zoster, influenza A, B, and *Mycoplasma* to be negative. CSF meningoencephalitis infectious panel returned negative. The red blood cell count and white blood cell count were within normal range. However, thrombocytopenia was observed with a count of 87×10^9/L (normal range: 100–300 $\times 10^9$/L). Laboratory analysis revealed elevated levels of C-reactive protein at 13.4 mg/L (normal range: <10 mg/L), procalcitonin (PCT) at 34.46 ng/mL (normal range: <0.5 ng/mL), tumor necrosis factor-α (TNF-α) at 22.2 pg/mL (normal range: 0.74–1.54 pg/mL), and interleukin (IL)-2 at 1460.87 pg/mL (normal level: <9.8 pg/mL). IL-6 and IL-10 levels were within normal limits. Serum myocardial enzyme spectrum was abnormal with creatinine kinase (CK) at 6330 U/L (normal range: 20–195 U/L), CK-MB at 238 U/L (normal range: <25 U/L), and LDH at 2151 U/L (normal range: 165–395 U/L). In addition, aspartate transaminase (AST) and alanine transaminase (ALT) levels were significantly elevated at 6544 U/L (normal range: 14–44 U/L) and 3882 U/L (normal range: 7–30 U/L), respectively. The prothrombin time was 23.8 s (normal range: 13.5 s), International normalized ratio was 1.98 (normal range: 0.8–1.25), antithrombin III was 0.68 (normal range: 0.80–1.30), fibrinogen degradation products level was 21.7 μg/mL (normal range: <5 μg/mL), and D-dimer was 10.13 μg/mL (normal range: <1 μg/mL). Furthermore, renal function was abnormal with urea at 8 mmol/L (normal range: 2.5–6.5 mmol/L) and creatinine at 48 μmol/L (normal range: 19–44 μmol/L). A respiratory pathogen PCR panel was conducted, which included testing for influenza A and B, rhinovirus, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella* bacteria Mora, Epstein–Barr virus, and *Mycoplasma*. The results of this panel were negative. Bacterial cultures of CSF and blood also yielded negative results. In addition, serum tests for electrolyte levels, glucose, ammonia, and ferritin were within normal range. Extensive autoimmune tests were performed with both serum and CSF, including tests for anti-*N*-methyl-d-aspartate, anti-myelin oligodendrocyte glycoprotein, anti-glutamic acid decarboxylase, and anti-GQ1b ganglioside IgG. All these autoimmune tests were negative. However, genetic susceptibility testing for *RANBP2* mutation was not conducted. Brain magnetic resonance imaging (MRI) [Figure 1] was performed, which revealed swelling and signal changes in various regions of the brain, including the bilateral dorsal thalami, right putamen, left temporal cortex, cerebellar vermis, and bilateral cerebellar hemispheres. Based on these findings, a diagnosis of ANE was made. In addition, the patient was diagnosed with combined disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS) based on laboratory findings. On the second day of admission, the child received immunotherapy with intravenous methylprednisolone at a dosage of 30 mg/kg/day for 5 days along with intravenous immunoglobulin (IVIG) at a dosage of 2 g/kg/day over 2 days. Remdesivir was administered for 5 days to treat SARS-CoV-2. Concurrent antimicrobials including empirical intravenous ceftriaxone, acyclovir, and oseltamivir were given until viral and bacterial studies returned negative results. Two days after the start of treatment, the child's temperature gradually returned to normal. After 10 days, inflammatory markers, coagulation profile, myocardial enzymes, and AST and ALT levels returned to normal. The Glasgow Coma Scale improved to 15, and improvements were seen in expressive aphasia and ataxia. The mRS score reduced to 2. Two weeks after treatment, a follow-up MRI of the brain [Figure 2] showed a significant reduction in the size of the lesions. The child was discharged home after 16 days with some residual deficits including upper limb dysmetria with intention tremor, mild aphasia, and dysarthria. At discharge, the mRS score was 1. One month after discharge, the child's neurologic function had fully recovered, and no recurrent episodes were observed during the 5-month follow-up period.

ANE is a rare parainfectious immune-mediated neurologic disorder. It is associated with various viruses, including influenza A and B, herpes simplex virus, and SARS-CoV-2, with influenza A being the most common. However, despite the high incidence of ANE in Asian countries, no case series of ANE has been reported during the latest outbreak of Omicron. Therefore, ANE has been identified as a rare complication of SARS-CoV-2 infection. So far, more than 20 cases of adult SARS-CoV-2–related ANE have been reported.[1] Main clinical manifestations of the condition include acute consciousness disorder or altered mental status, seizures, speech disturbances, or motor disorder within 1 week of the onset of fever. It is worth noting that all previously reported cases were previously healthy individuals with no underlying disease. Only one case was complicated with DIC,[2] and no case was associated with MODS. The clinical features of our patient were consistent with those reported previously. It is important to mention that mild lymphocytic-predominant pleocytosis has been described in COVID-19–associated ANE.[3] However, in the case of our patient, there was a predominance of neutrophils. In addition, the present case exhibited MODS with DIC, liver dysfunction, and acute renal impairment.

The most widely accepted mechanism of ANE is currently believed to be virus-induced cytokine storm rather than direct viral invasion itself.[4] In severe cases of COVID-19, cytokine storm is thought to be the primary cause of complications in multiple organs and death.[5]

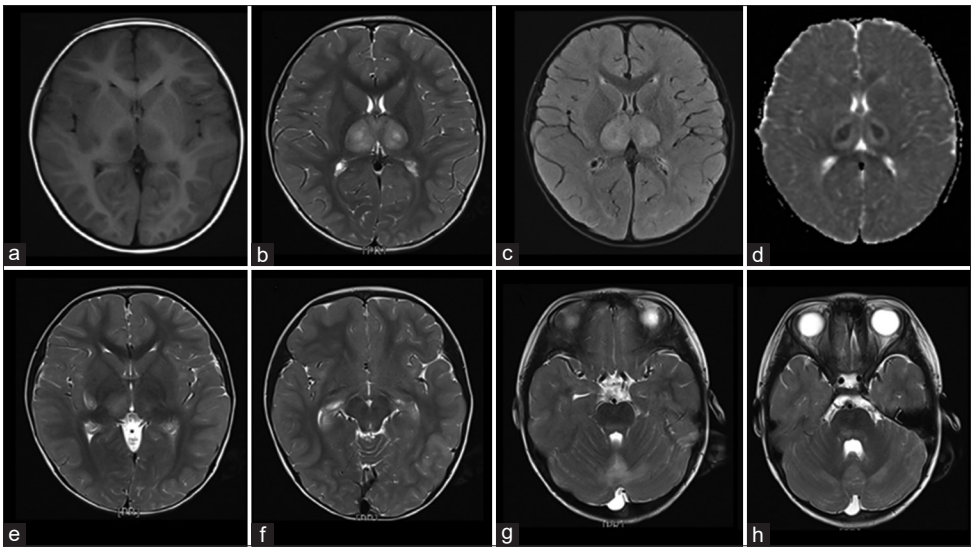

Figure 1: Axial T1WI, T2WI, T2-FLAIR, and ADC map on bilateral basal ganglia level. (a–d) Bilateral dorsal thalami are swollen with slight hypointensity on T1WI and slight hyperintensity on T2WI. Small nodules in the center of the lesions show a lower signal on T1WI and a higher signal on T2WI with slight hyperintensity on T2-FLAIR (c). Axial ADC map (d) shows a "dual-color pattern," which indicates arterial, venous, and capillary congestion and cytotoxic edema of oligodendrocytes in the center of the lesion and peripheral exudation in the periphery of the lesion. Similar characteristic lesions are seen on the right putamen (e). (f–h) Slightly swollen and slightly hyperintense T2WI in the left temporal cortex, vermis, and bilateral cerebellar hemispheres, respectively. T1WI: T1 weighted image, T2WI: T2 weighted image, T2-FLAIR: T2 fluid attenuated inversion recovery, ADC: Apparent diffusion coefficient

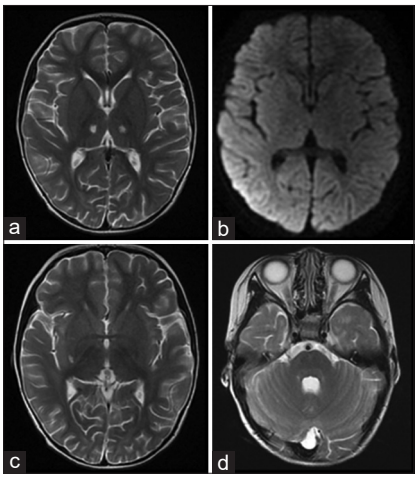

Figure 2: Two weeks after treatment, an MRI of the brain (a and b) showing no obvious swelling in the bilateral dorsal thalamus, obvious reduction in the scope of the lesions, and no limited diffusion. (c and d) Lesions of the right putamen, cerebellar vermis, and bilateral cerebellar hemispheres are significantly reduced. MRI = magnetic resonance imaging

In our case, the immune-mediated mechanism is supported by the significant elevation of TNF-α, IL-2, PCT, and LDH levels in the patient's serum. The patient also showed remarkable improvement after receiving high-dose methylprednisolone and IVIG therapy, which further supports the immune-mediated mechanisms.

In conclusion, our patient's case adds to the limited number of reports on ANE associated with SARS-CoV-2 infection. This supports the notion that cytokines play a role in the immune-mediated mechanism of ANE. Our report, along with the literature review, emphasizes the importance of early diagnosis and prompt administration of immunomodulatory therapy specific to ANE to improve neurologic outcomes. Further research is needed to investigate SARS-CoV-2–related ANE or central nervous system pathology, the immune-mediated process, and therapeutic implications. This research requires national and international collaboration to collect large, organized datasets.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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