CASE REPORT

COVID-19-Associated Acute Necrotizing Encephalopathy: A Case Report

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Abstract

COVID-19 is a pandemic disease in which most patients have pulmonary symptoms. However, several cases of CNS involvement associated with COVID-19 have been reported.

Acute necrotizing encephalopathy of childhood (ANEC) is a rare CNS complication of viral infections such as influenza, herpes virus, and COVID-19, leading to high mortality and morbidity rates. Several cases of COVID-19-associated acute necrotizing encephalopathy (ANE) have been reported since March 2020 in adults, with just a few cases in pediatrics.

This article reports a 5-month-old child who presented with seizures, with the final diagnosis of ANE as a complication of COVID-19.

MRI findings of ANEC, as reported in most COVID-19-associated ANEC case reports, involve bilateral, symmetric, multifocal lesions in the central thalami. Moreover, the brainstem, cerebral white matter, and cerebellum could be affected.

The prognosis of COVID-19-associated ANE is poor, leading to neurologic dysfunction or mortality. COVID-19-associated ANE cases must be reported, especially in pediatrics, with detailed clinical history, laboratory data, and radiologic findings to introduce diagnostic criteria, prognosis, and a management protocol.

Keywords: COVID-19, Acute Necrotizing Encephalopathy, Pediatric, Case Report
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Introduction

COVID-19 is a novel, rapidly emerging RNA virus announced as a pandemic disease in March 2020 (1). Since then, several cases of CNS involvement associated with COVID-19 have been reported. Patients may present with neurologic symptoms such as headaches, dizziness, epilepsy, altered mental status, delirium, ataxia, limb paralysis or weakness, neuralgia, abnormal sensation, and neuropsychiatric symptoms, which could be signs of life-threatening conditions like acute necrotizing encephalopathy (ANE), encephalitis, or meningitis (2, 3).

There are several case reports of COVID-19-associated ANE in adults, with just a few cases in pediatrics. This article reports a case of COVID-19-associated encephalopathy in a 5-month-old child who presented with seizures.

Case Presentation

A 5-month-old infant was referred to the hospital for repair surgery of total anomalous pulmonary venous connection and ventricular septal defect (TAPVC-VSD), diagnosed following developmental delay and failure to thrive. He was the third child of nonconsanguineous parents and was born at full term by caesarian section with no perinatal complication or abnormal prenatal ultrasound findings. All family members, including older siblings and close relatives, were healthy. His parents reported that he had never experienced seizures or other neurological symptoms.

The initial COVID-19 PCR test was negative, and the patient was afebrile with no remarkable finding on physical examination except mild wheezing while crying and mid-systolic murmur due to underlying cardiac anomaly.

The patient became febrile and experienced two episodes of seizures a few days before surgery.

Immediately after the seizure, the patient was intubated because of decreased oxygen saturation during the seizure. Oxygen saturation was maintained in the normal range, and anticonvulsant drugs were administered. A COVID-19 PCR test was requested again, which was positive. The patient's lab test showed elevated liver enzymes without hyperammonemia or hyperbilirubinemia (AST=60 and ALT=65 with no significant decrease during hospitalization). Other lab tests were in the normal range, except for a slight electrolyte imbalance, which was carefully treated.

Brain MRI was also requested eight days later and showed confluent areas of high signal in the subcortical white matter on coronal T2W imaging (Figure 1, C) due to hypomyelination. On T1W images, multifocal cortical hemorrhage and cortical necrosis in both hemispheres were noted (Figure 1, A and B). Restricted diffusion on DWI in the thalami and splenium of the corpus callosum was visible due to necrosis (Figure 2). The final diagnosis was ANE.

Cardiac surgery was postponed. The patient was treated with high-dose steroids and IVIG. He succumbed twenty days later.

Discussion

COVID-19-affected patients may present with neurologic symptoms due to life-threatening conditions such as ANE, encephalitis, or meningitis. Although the pathogenesis of neurologic involvement is not fully understood, several possible mechanisms are suggested.

A case report of an 11-year-old child who presented with status epilepticus and a final diagnosis of COVID-19-associated encephalitis suggests that

Tabel 1. Diagnostic criteria Acute Necrotizing Encephalopathy of Childhood (ANE)

1. Acute encephalopathy following a viral febrile disease Rapid deterioration in the level of consciousness Convulsions
2. No CSF pleocytosis. Increase in CSF protein commonly observed
3. CT or MRI evidence of symmetric, multifocal brain lesions Involvement of the bilateral thalami Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum and cerebellar medulla No involvement of other CNS regions
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia
5. Exclusion of resembling diseases A. Differential diagnosis from clinical viewpoints. Overwhelming bacterial and viral infections, and fulminant hepatits; toxic shock, hemolytic uremic syndrome and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke. B. Differential diagnosis from radiological viewpoints. Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy, and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leucoencephalitis, other types of encephalitis and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

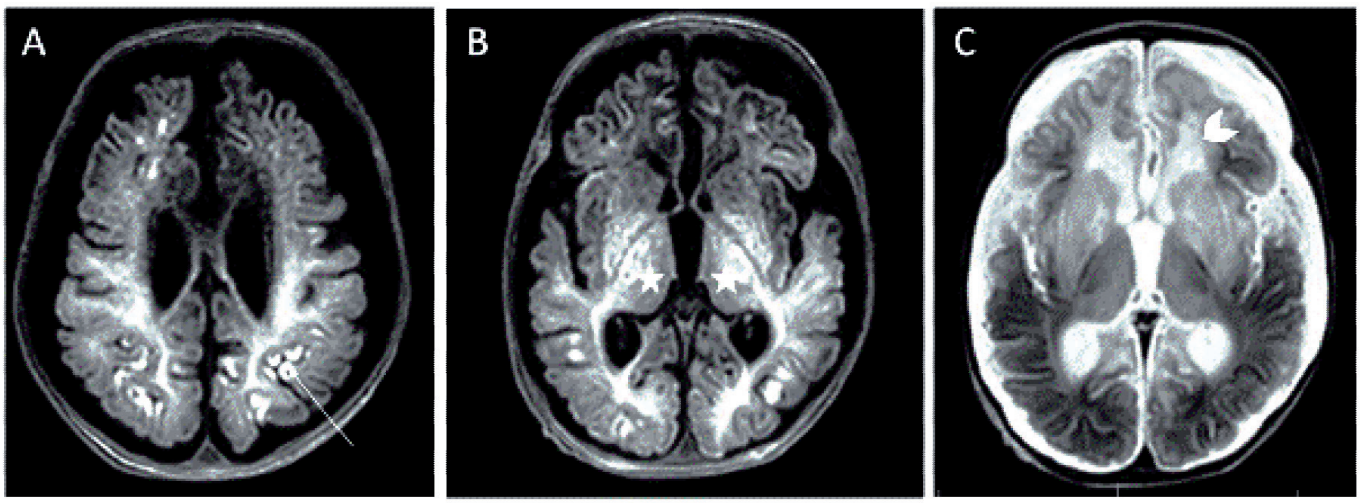

Figure1. Axial T1W(A&B) showed cortical hemorrhage in right frontal and both temporoparietal lobes (arrow) and axial T2W(C) manifested hypomyelination(arrow head).Symmetric hyperintensity in basal ganglia is visible(star).

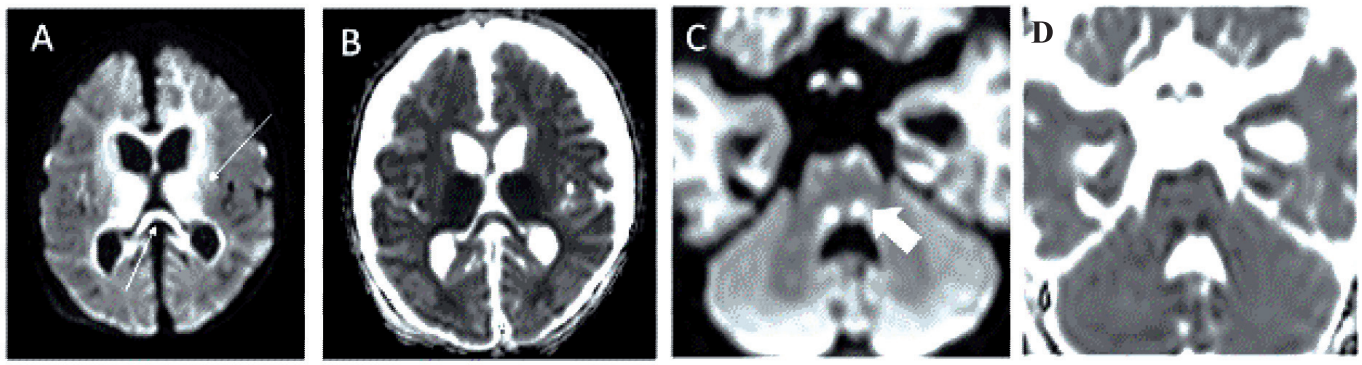

Figure2.Diffusion restriction is notable in thalami , spleinum of corpus callosum(A&B; arrow) and central tegmental tract (C&D; thick arrow).

direct brain infection or an autoimmune process could be possible (4). In another study, the virus was present in the brain tissue at autopsy (5).

COVID-19 triggers cytokine storm syndrome, cytokine dysregulation, and increased inflammatory cells due to immunopathogenic responses to the virus (6, 7). The virus causes overactivation of the immune system to attack itself (8), leading to systemic inflammation response syndrome, multi-organ failure, increased vascular permeability, and brain edema (9, 10). This inflammatory response also promotes atherosclerosis, plaque rupture, thrombosis, and ischemic or hemorrhagic damage (11). In this setting, markers for systemic inflammation are expected to be elevated.

Another possible mechanism involves angiotensin-converting enzyme II (ACE-II) receptors. Surface spike proteins of the virus bind to the ACE-II receptors present in several organs, including brain vascular endothelial cells, decreasing the ACE-II receptor expression and diminishing its vasoprotective effect. It could be the reason for vascular inflammation, atherosclerosis, and microthrombosis (12-14).

Hypoxia due to viral pneumonia and ARDS could result in acidosis, intracranial blood vessel dilation, increased cerebral capillary pressure and permeability, interstitial brain edema, increased intracranial pressure, and decreased ATP production. Hypoxia can also alter cellular metabolism, leading to anaerobic glycolysis, intracellular accumulation of lactic acid, production of free radicals, and blood-brain barrier dysfunction (15-17). Finally, hypoxia leads to neuronal and astroglial necrosis, apoptosis, and neurocognitive deficits (18).

Hypoxemia creates a hypercoagulable state by producing inflammatory factors, catecholamine, tissue factors, and platelet aggregation. Sympathetic overactivity, endothelial damage, and higher levels of erythropoietin and polycythemia result in hypercoagulability and an increased incidence of cerebrovascular disease (19).

ANE is a rare CNS complication of viral infections such as influenza, herpes virus, and COVID-19, leading to high mortality and morbidity rates. It is characterized by the rapid onset of neurological symptoms associated with hemorrhagic lesions in the deep gray matter in a post-infectious setting (20, 21).

Several cases of COVID-19-associated ANE have been reported since March 2020 in both pediatrics and adults. ANE predominantly affects children, but most COVID-19-associated ANE case reports involve the adult population (22-29), with just a

few cases in pediatrics (30, 31), which is likely because pediatrics account for only 1–5% of diagnosed COVID-19 cases (32). The Prognosis of COVID-19-associated ANE is poor, leading to neurologic dysfunction (26, 28) or mortality (8, 23, 25-27, 29).

Radiologically, MRI findings of ANE, as reported in most COVID-19-associated ANE case reports, involve bilateral, symmetric, multifocal lesions in the central thalami. Moreover, the brainstem, cerebral white matter, and cerebellum could be affected. (22-26)

MRI findings of the present case report also revealed the involvement of both thalami, parietal lobes, splenium of the corpus callosum, corticospinal tract, frontotemporal lobes, left temporal lobe, basal ganglia, and brain stem, and cortical necrosis with some superimposed cortical hemorrhage.

The diagnostic criteria of ANE (33) are mentioned in Table 1. The patient fulfills the criteria except for the second item, as CSF analysis was not performed. Considering his rapid deterioration in consciousness, convulsions, typical MRI findings, and increased serum aminotransferases (an important unique finding in ANE), the most probable diagnosis is ANE. Other differential diagnoses can be excluded based on the patient's history and imaging findings. Hypoxic ischemic encephalopathy could be excluded as the patient was under close observation, and his oxygen saturation was in the normal range during hospitalization.

In Conclusion

During this pandemic, physicians must pay attention to the neurologic symptoms of affected patients since early diagnosis and treatment result in lower mortality and morbidity rates (3). COVID-19-associated ANE cases should be reported, specifically in pediatrics, with detailed clinical history, laboratory data, and radiologic findings to introduce diagnostic criteria, prognosis, and a management protocol.

ANEC: Acute Necrotizing Encephalopathy of Childhood

ANE: Acute Necrotizing Encephalopathy

TAPVC: Total anomalous pulmonary venous connection

VSD: Ventricular Septal Defect

Acknowledgment

None

Author's Contribution

RS was the attending doctor of the patient.

FZ was the consultant radiologist during the patient's hospitalization, who reported MRI images and revised the article.

SH and FF contributed to review medical reports of the patient, drafting, and revision of the article.

All authors approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests

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