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Acute Necrotizing Encephalopathy Associated with Coronavirus Disease 2019 in an Infant

Mariha Khan, MD¹, Samhita Bhattarai, MD¹, Thomas G. Boyce, MD, MPH¹, Reyaad A. Hayek, MD², Sergey I. Zhadanov, MD, PhD², Elisabeth E. Hooper, MD¹, Edward G. Fernandez, MD¹, and Monica A. Koehn, MD³

A 5-week-old infant born at term was diagnosed with acute necrotizing encephalopathy associated with severe acute respiratory syndrome coronavirus 2 as evidenced by clinical presentation, neuroimaging, and cerebrospinal fluid studies. Our patient was treated with high-dose intravenous methylprednisolone, tocilizumab, and intravenous immunoglobulin with significant short-term clinical improvement but long-term sequelae. (*J Pediatr* 2022;247:160-2).

Multiple reports of neurologic involvement in patients, primarily adults, with coronavirus disease 2019 (COVID-19) have been reported; these include encephalopathy, anosmia, ageusia, peripheral neuropathy, plexopathy, seizure, meningitis, and stroke.¹ In addition, cases of acute necrotizing encephalopathy (ANE) have been reported in severe COVID-19 infection in adults and one in the pediatric population.^{2,3}

ANE was originally described in 1995 as a complication of viral respiratory tract infection in pediatric patients of Japanese descent, with RNA viruses implicated in the majority of cases.⁴ The hallmark of ANE is multiple necrotic brain lesions showing a symmetric distribution. We present a case of ANE as the initial presentation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in an infant.

Case Presentation

A previously healthy, 5-week-old female infant born at 39 weeks of gestation was brought to medical attention after 3 days of decreased oral intake, with irritability, progressive lethargy, and episodic bilateral lower extremity stiffening. There was no history of fever, respiratory, or gastrointestinal symptoms. The infant had not received any antipyretic or anti-inflammatory medication after symptom onset. She had episodic generalized clonus of the upper extremities and stiffening of the lower extremities for 12 hours before presenting to the emergency department. A loading dose of intravenous levetiracetam was given upon arrival. She was promptly admitted to the pediatric intensive care unit.

Initial physical examination revealed an afebrile female infant weighing 4.3 kg with no dysmorphic features or signs of trauma. She was encephalopathic with limited arousal to

tactile, visual, and auditory stimuli. She was inconsolable, with irritability and generalized rigidity in all extremities. Occasional arching of the back was observed with enhanced irritability. Her eyes were open and she had nystagmoid eye movements. Pupils were 4-5 mm, equal, and reactive to light.

Complete blood count, C-reactive protein, and procalcitonin levels were normal. Basic metabolic panel showed elevated serum sodium of 146 mmol/L (reference: 133-144 mmol/L), potassium of 6.5 mmol/L (3.3-5.9 mmol/L), and chloride of 116 mmol/L (96-109 mmol/L). Aspartate transaminase and alanine transaminase levels were mildly elevated at 91 U/L (3-57 U/L) and 92 U/L (6-30 U/L), respectively. Serum creatinine kinase was elevated at 403 U/L (33-157 U/L), and ammonia was 67 μ mol/L (16-53 μ mol/L). SARS-CoV-2 polymerase chain reaction (PCR) performed on a nasopharyngeal swab was positive. A respiratory pathogen PCR panel including influenza A, B, and *Mycoplasma* was negative.

Computed tomography of the head without contrast revealed symmetric edema within the bilateral thalami, caudate nuclei, and insula, suggestive of profound ischemic injury (not shown). Magnetic resonance imaging (MRI) of the brain (Figure, A and B) confirmed extensive areas of cytotoxic edema in the bilateral thalamic nuclei and adjacent posterior limb of the internal capsules sparing the pulvinar. The caudate heads and the subinsular white matter, temporal lobes, and both amygdaloid nuclei showed similar abnormality. Gradient echo images showed mild signal dropout within the thalami. Major flow voids in the arteries of the base of the skull base and dural sinuses were preserved without evidence for major vascular occlusion.

Cerebrospinal fluid (CSF) revealed elevated protein of 199 mg/dL, white blood cell count of 2/ μ L with 91% monocytes, and glucose of 56 mg/dL. CSF PCR for herpes simplex virus, SARS-CoV-2, enterovirus, and parechovirus were negative. Repeat SARS-CoV-2 PCR on a nasopharyngeal

ANE	Acute necrotizing encephalopathy
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
IL-6	Interleukin-6
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

From the Departments of ¹Pediatrics, ²Radiology, and ³Neurology, Marshfield Clinic Health System, Marshfield, WI

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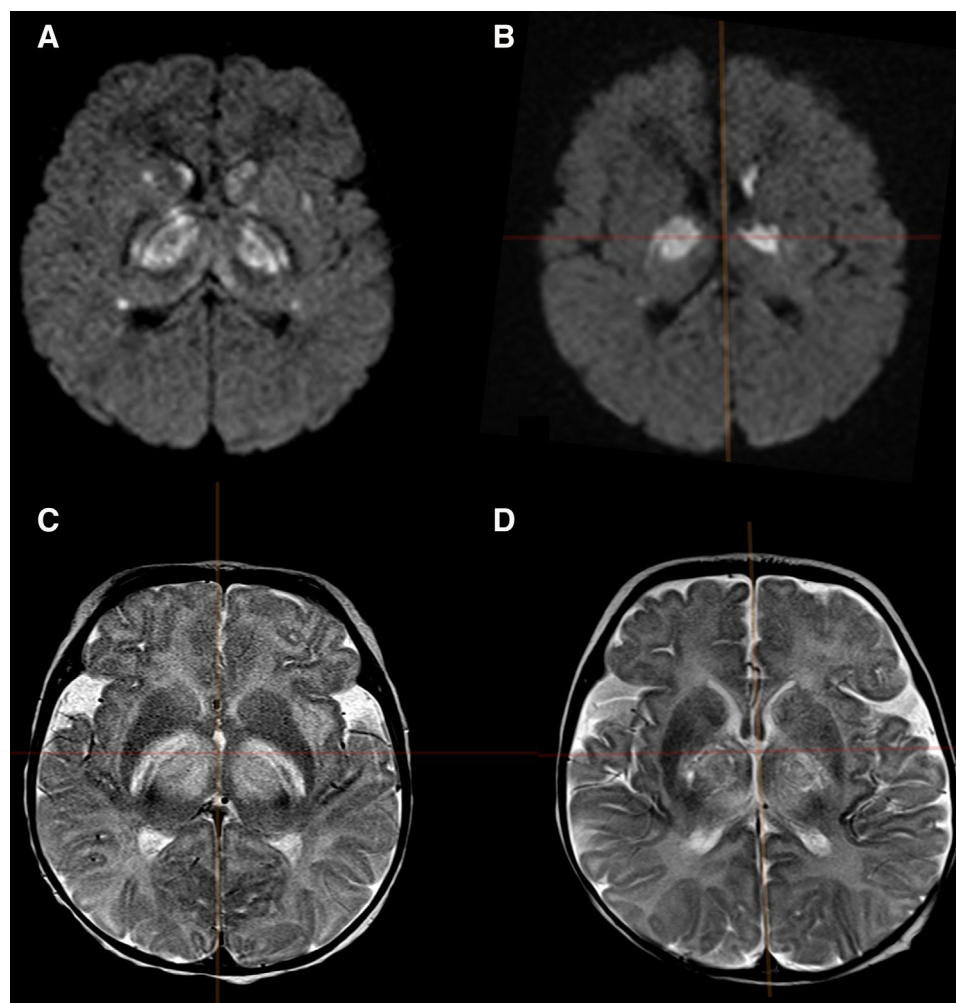


Figure. Representative magnetic resonance images (MRIs) from admission and on day 9 of hospitalization. **A** and **B**, Admission MRI. **A**, Diffusion-weighted and **B**, T2 images reveal bilateral symmetric edema in the thalami and caudate heads. There is also involvement of the amygdala, temporal lobes, and external capsules (not shown). **B** and **C**, Day 9 MRI. **C**, Diffusion and **D**, T2 images demonstrate overall reduction in cytotoxic edema with areas of signal abnormality being more confined to dorsomedial thalami with more evident necrotic change. There is significant improvement in right caudate head, temporal, and insular parenchyma (not shown).

swab was positive. SARS-CoV-2 IgG performed on day 3 of hospital admission was negative. Genetic testing for mutations in the RANBP2 gene was negative.

Based on clinical presentation, neuroimaging, and CSF findings, a diagnosis of acute necrotizing encephalitis associated with SARS-CoV-2 was made. Given the severity of generalized rigidity, encephalopathy, and the concern for poor neurologic outcome, the patient was treated with intravenous tocilizumab 12 mg/kg once, high-dose methylprednisolone 30 mg/kg for 5 days, and intravenous immunoglobulin 2 g/kg. No significant adverse reaction occurred. To characterize initial tremors with increased tone, video electroencephalogram monitoring was initiated immediately on admission and was performed for 48 hours. This showed poor interhemispheric synchrony and poor regional and state specific patterns for age but no evidence of seizures.

Minimal respiratory support was provided transiently with 2 L of 21% fraction of inspired oxygen for comfort, but intubation was not required. Sedation with dexmedetomidine improved dystonic posturing, rigidity, and irritability. With decreased posturing and irritability, dexmedetomidine sedation was weaned over 5 days, following which oral clonidine was initiated.

The neurologic status and rigidity improved steadily. On day 8 of hospitalization, she was transferred to the pediatric medical-surgical unit, where she tolerated oral feedings well. Multimodality therapies were associated with improved range of motion in the lower extremities, and oral clonidine was transitioned to gabapentin.

Repeat MRI of the brain (**Figure**, C and D) on hospital day 9 showed near-complete resolution of brain edema in the insula and temporal regions. Diffusion signal abnormality persisted but now was confined to the thalami and left

caudate head, with more apparent intrinsic T1 signal shortening in the dorsomedial thalamic nuclei implying necrosis. The patient was discharged to home on hospital day 20.

At the patient's 8-month follow up, she was not able to sit independently without support, and neck support was poorly sustained. Muscle tone was increased without any clonus. At 12-month follow up, the patient continued to have poor head and truncal support, spastic quadriparesis, and asymmetric tonic neck reflex. Overall, the patient had a developmental age of 3 months with features consistent with cerebral palsy.

Discussion

Although the respiratory tract is the primary target of SARS-CoV-2 infection, neurologic consequences of infection have been recognized, and neurologic symptoms contribute significantly to morbidity in adult patients.⁵

Our patient with ANE as a manifestation of SARS-CoV-2 infection in a young infant presented with profound encephalopathy, rigidity, and dystonia. She also had typical features of ANE on MRI of the brain, including symmetric involvement of the thalami, caudate heads, internal capsules, and temporal lobes with areas of necrosis and probable hemorrhage.²

ANE is a rare parainfectious, rapidly progressive condition often resulting in devastating neurologic sequelae. ANE is usually triggered by a preceding viral infection, with influenza A and B, varicella, and human herpes virus 6 most commonly associated ANE.⁶ ANE is not believed to be due to a direct viral infection of the central nervous system, but rather a manifestation of an immune-mediated process with increased proinflammatory cytokines, especially interleukin-6 (IL-6).⁶ PCR analysis on the CSF in patients with ANE usually fails to detect viral nucleic acid. As in our patient, CSF protein typically is elevated, but pleocytosis is absent. Common clinical manifestations of ANE are seizures, encephalopathy, and motor deficits, with rapid progression over a few days and a case-fatality rate as high as 30% despite aggressive immune-modulatory therapy. Patients who survive generally have a poor neurologic outcome.⁶

Most cases of ANE are sporadic and nonrecurrent; however, familial cases associated with a *RANBP2* missense mutation on chromosome 2q11-13, termed ANE-1, is inherited in an autosomal dominant pattern with variable penetrance. The exact underlying pathophysiology is unknown, but it has been postulated that the neurologic injury in ANE-1 is due to changes in permeability of vessel walls due to high circulating levels of cytokines in these patients.⁶ Children with ANE should be tested for the presence of a mutation in *RANBP2* to determine whether they are at risk for recurrent episodes of ANE.

A dysregulated host immune response is a widely recognized mechanism of excessive systemic inflammation in patients hospitalized with COVID-19 and multiorgan

inflammatory syndrome can be associated with adverse clinical outcomes including brain injury.⁷ Upregulated cytokine response has been implicated in ANE in severe viral infection with increased blood IL-6 levels correlating strongly with poor outcome.⁸ In addition, case studies in children with ANE due to influenza have shown clinical and radiologic improvement after a single dose of tocilizumab, a monoclonal antibody targeting the IL-6 receptor.⁹

It is impossible to determine with certainty whether our patient's initial improvement was due to corticosteroid, intravenous immunoglobulin, tocilizumab, some combination of these agents, or the natural history of the disease. Further delineation of effective treatments for this condition would require randomized trials, which are not practical given its rarity. MRI remains crucial in prompt recognition of this rare complication, allowing for supportive care and possibly effective specific therapy with a goal of improved neurologic outcome. ■

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Reprint requests: Reprint requests: Monica Koehn, MD, Department of Neurology, Marshfield Clinic Health System, 1000 N Oak Ave, Marshfield, WI 54449. E-mail: koehn.monica@marshfieldclinic.org

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