Post–COVID-19 Acute Disseminated Encephalomyelitis in a 17-Month-Old

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Neurologic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pediatric patients have been reported in the acute and postinfectious stages of coronavirus disease 2019. Acute disseminated encephalomyelitis (ADEM) typically presents in children after a viral illness at a mean age of 3 to 7 years. A total of 60% to 90% of literature-reported pediatric patients with ADEM have minimal to no neurologic deficits at long-term follow-up. We present a 17-month-old developmentally typical girl with parental complaints of irritability, upper extremity weakness, and gait disturbance. She presented to the hospital afebrile and irritable with right-sided nasolabial fold flattening, neck stiffness, left upper extremity rigidity, right upper extremity paresis, bilateral lower extremity hyperreflexia, and truncal ataxia. During her hospital course, she became somnolent with autonomic instability and was transferred to intensive care. Contrasted brain MRI revealed diffuse patchy T2 hyperintensities without contrast enhancement. Nasopharyngeal SARS-CoV-2 polymerase chain reaction and serum antibody testing results were positive. Cerebral spinal fluid analysis was unremarkable. Respiratory viral panel and autoimmune encephalitis and demyelinating disorders panel results were negative. She was started on high-dose methylprednisolone and intravenous immunoglobulin, with improvement in mental status, focal deficits, and ambulation. After hospital discharge, she received inpatient rehabilitation for 2 weeks and at 2 month follow-up had a full neurologic recovery. We report the youngest case of postinfectious ADEM due to SARS-CoV-2 in a toddler. Early recognition of autoimmune and inflammatory complications of SARS-CoV-2 is vital for early aggressive immunomodulatory treatment and, consequently, improved morbidity in these patients.
of fever, malaise, vomiting, and/or headaches. Neurologic symptoms are multifocal and correlate with radiologic lesions in the brain and/or spinal cord, clinically presenting as ataxia, encephalopathy, hemiplegia, hemiparesthesias, visual changes, seizures, or cranial nerve palsies. This neurologic decline occurs rapidly within days to weeks after the prodromal illness; symptoms in the majority of patients do not progress beyond 3 months. We present a case of ADEM secondary to COVID-19 in a 17-month-old girl who fared well with early and aggressive immunomodulating therapy, which included high-dose corticosteroids and intravenous immunoglobulin (IVIG) treatments.

CASE

A 17-month-old African American, non-Hispanic, previously healthy, and developmentally typical girl presented to the emergency department with fatigue, progressively worsening weakness, and unsteady gait. She had 5 days of fever; ∼13 days before presentation, with a maximum temperature of 38.9°C without associated upper respiratory or gastrointestinal symptoms. After fever resolution, her parents noticed progressive fatigue, decreased communication, and difficulty feeding herself, walking, and sitting without support. She presented to the hospital with parental complaints symptoms of irritability, weakness of upper extremities, and gait disturbance. She was found to be afebrile but irritable, with subtle right-sided nasolabial fold flattening, significant neck stiffness with a positive Brudzinski’s sign, left upper extremity rigidity, right upper extremity paresis, bilateral lower extremity hyperreflexia, and truncal ataxia.

In the initial evaluation, an electrocardiogram was included, with normal sinus rhythm, possible right atrium enlargement, and left ventricular hypertrophy. A transthoracic echocardiogram performed in the PICU was normal. Laboratory evaluation noted elevated inflammatory markers, including an erythrocyte sedimentation rate of 25 mm/hour, which increased to 40 mm/hour within 2 days, and lactate dehydrogenase of 406 IU/L. Normal serum studies included complete blood count, comprehensive metabolic panels, prothrombin time and international normalized ratio, partial thromboplastin time, ferritin, D-dimer, brain natriuretic peptide, troponins, ammonia levels, and creatine kinase. An MRI of the brain with and without gadolinium contrast revealed multifocal hyperintense T2 fluid-attenuated inversion recovery (FLAIR) signals in bilateral subcortical and periventricular white matter without contrast enhancement (Fig 1).

An MRI of the whole spine without contrast was unremarkable. Cerebral spinal fluid (CSF) and serum studies were performed before the initiation of high-dose methylprednisolone. CSF analysis revealed mild pleocytosis with lymphocytic predominance: 5 per mcL white blood cells (81% lymphocytes, 19% monocytes), 1 per mcL red blood cell, glucose of 58 mg/dL, and protein of 17 mg/dL. The CSF had zero oligoclonal bands, with a normal immunoglobulin G (IgG) index and IgG synthesis rate. The CSF polymerase chain reaction (PCR) was negative for enterovirus. Other infectious studies were not obtained, given the limited CSF sample. Serum study results for antinuclear antibody, Aquaporin 4 antibodies, myelin oligodendrocyte glycoprotein (MOG) antibodies, and thyroid peroxidase antibodies were negative. CSF and serum bacterial culture results were negative. An upper respiratory viral PCR panel via nasopharyngeal swab and a stool PCR were negative for enterovirus and rotavirus antigen. Results from a SARS-CoV-2 PCR via nasopharyngeal swab and serum

![FIGURE 1](A, An MRI brain T2 FLAIR axial image revealing diffuse hyperintensities in the subcortical white matter. **B**, An MRI brain T2 axial image revealing diffuse patchy T2 hyperintensities. **C**, An MRI brain T2 FLAIR coronal image revealing hyperintensities in the cortical and subcortical white matter.)
SARS-CoV IgG antibody testing were both positive. Infection was evaluated by using Hologic Aptima SARS-CoV-2 assay (sensitivity: >90%) and serum SARS-CoV IgG antibody (sensitivity: 84%; specificity: 100%) testing performed by Abbott Laboratories.10,11 The patient’s parents were health care workers. Her father tested positive for SARS-CoV-2 3 months before the patient’s presentation.

On day 2 of hospitalization, she was transferred to the PICU because of increased lethargy, autonomic instability, and concern for seizures. Electroencephalography revealed diffuse slowing, consistent with encephalopathy, but no seizures or epileptiform activity. Because of clinical deterioration, IVIG 2 g/kg divided over 4 days was initiated, in addition to completion of a 5 day course of high-dose IV methylprednisolone (30 mg/kg per day).

On day 5 of hospitalization, she was transferred to the general pediatric floor. Her examination continued to improve. She was alert, attentive to the examiner, able to sit unsupported, and able to walk with support. She was discharged to inpatient rehabilitation for 2 weeks, with a 6-week oral prednisone taper. A neurologic examination at 2 month postdischarge neurology follow-up had completely normalized.

**DISCUSSION**

There is a growing body of evidence of neurologic sequelae secondary to COVID-19 disease. Common neurologic symptoms during an active infection include headache, anosmia, and myalgias. Severe active COVID-19 disease has been associated with viral meningitis, hypoxic ischemic encephalopathy, acute cerebrovascular insults, and acute necrotizing hemorrhagic encephalopathy.12,13 Additional postinfectious sequelae have included Guillain-Barre syndrome and ADEM. Neurologic manifestations in pediatric populations mimic those seen in adult populations but also include febrile seizures, acute flaccid myelitis, and a single pediatric report of ADEM in an adolescent.2,3 ADEM is an autoimmune disorder of the central nervous system (CNS), with suspected pathogenesis from activation of the immune system by environmental triggers, such as infection in genetically susceptible individuals.14,15 Myelin autoantigens, such as myelin basic protein, proteolipid protein, and MOGs, are implicated in the pathogenesis.15 These proteins share antigenic properties with those of an infectious pathogen; this molecular mimicry triggers an autoimmune response leading to demyelination of the CNS.14 Antiviral antibodies or a cell-mediated response to these pathogens can cross-react with the myelin antigens, leading to ADEM.14-16

In North America, the estimated incidence of ADEM is 0.2 to 0.4 per 100 000 per year in pediatric patients.5,17 ADEM is primarily seen in children, between 3 and 7 years old, and young adults.6,18,19 There is a boy to girl predominance of 1 to 0.8.7 It is frequently associated with infections and recent immunization. In 64% to 93% of ADEM cases, a preceding infection was identified.4,5,7,8,20 In adults, COVID-19-associated encephalopathy has been reported in up to 37% of some infected cohorts, but the etiology has varied among toxic-metabolic, seizures, demyelinating disease, and potentially direct infection.21 The proposed mechanisms of neuroinvasion include trans-synaptic transmission retrograde from peripheral nerve terminals to CNS tissues as in other coronaviruses. SARS-CoV-2 spreads across the blood–brain barrier via angiotensin-converting enzyme 2 receptors required for viral cell entry into brain endothelium.22 COVID-19 cases have been exceedingly low in pediatric populations, but cases of serious neurologic manifestations have been reported in isolated cases.2,3,23,24 Kim et al25 recently proposed that pediatric populations may be less susceptible to neurologic complications of SARS-CoV-2 because angiotensin-converting enzyme 2 is expressed the lowest in younger children.

Many other causes of encephalopathy can mimic ADEM, and a complete evaluation is indicated.26 Encephalopathy has a broad differential diagnosis and commonly results from an infectious agent, such as a virus, bacteria, or arthropod-borne microorganism.5,26 If the CSP reveals nonspecific abnormalities and there is evidence of white matter lesions on an MRI, other inflammatory demyelinating disorders should be considered.17,27 Common demyelinating disorders in children include: multiple sclerosis (MS), MOG antibody-associated disease, neuromyelitis optica spectrum disorder, and clinically isolated syndromes (optic neuritis, transverse myelitis, and brainstem encephalitis).17,27

In pediatric patients, demyelinating disease etiologies can be difficult to stratify because many of the initial presentations overlap among disease and syndromes. Among patients initially diagnosed with ADEM, ~50% were found to have MOG antibodies, whereas aquaporin-4 antibodies traditionally associated with neuromyelitis optica spectrum disorder are rarer in children.28 MOG antibody–positive spectrum disease is typically monophasic; however, persistent presence of antibodies has been associated with relapsing disease.29,30 Children appropriately diagnosed with ADEM infrequently progress to...
meet the criteria for MS. The time of presentation, our patient did not meet the revised 2017 McDonald criteria for MS. Moreover, the incidence of MS is rare in children <12 years of age. At 2-month follow-up, our patient had returned to baseline, with a nonfocal neurologic examination. We do recognize that her follow-up interval was limited in duration but followed the typical clinical course for ADEM. Additionally, given our patient’s resolution of focal deficits, reimaging was deferred to limit exposure to sedation.

Further consideration in the differential diagnosis of ADEM includes other infectious and autoimmune causes. Acute viral encephalitis was considered in our patient but thought to be less likely because she was afebrile on admission. Screening respiratory viral panel and CSF culture results were negative. The patient was unlikely to have had an active SARS-CoV-2 infection at presentation, given the time line of parental exposure and the preceding febrile illness, which had resolved. Furthermore, our patient’s time frame of exposure, febrile illness with resolution, and hospital presentation are more clinically suggestive of postinfectious ADEM. Other etiologies, such as small vessel childhood primary angiitis of the CNS, malignancy, and hemophagocytic lymphohistiocytosis were considered but thought less likely, given the presentation.

Early intervention is crucial for early recovery in patients with ADEM. First-line therapy for ADEM is high-dose glucocorticoids for a 5-day course, which can be given concomitantly with antibiotics and antiviral agents, until infection is ruled out. Other immune therapies, including IVIG and plasma exchange, should be considered in fulminant disease, steroid-unresponsive cases, or relapses, as second-line therapy. Clinical improvement occurs within days of immunomodulating therapy initiation. Many children diagnosed with ADEM have a full recovery.

CONCLUSIONS
ADEM with typical neuroimaging findings of scattered T2 hyperintensities primarily affecting the deep white matter can potentially occur after COVID-19 infection in toddlers. Immunomodulatory treatment with high-dose IV methylprednisolone and IVIG was effective in this case, with a full neurologic recovery noted at 12 weeks, although the follow-up duration was limited. Health care providers should consider ADEM when evaluating a child with encephalopathy and neurologic deficits after recovering from COVID-19.

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ABBREVIATIONS
ADEM: acute disseminated encephalomyelitis
CNS: central nervous system
COVID-19: coronavirus disease 2019
CSF: cerebral spinal fluid
FLAIR: fluid-attenuated inversion recovery
IgG: immunoglobulin G
IVIG: intravenous immunoglobulin
MOG: myelin oligodendrocyte glycoprotein
MS: multiple sclerosis
PCR: polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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