CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Encephalopathy and bilateral thalamic lesions in a child with MIS-C associated with COVID-19

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Neurology® 2020;95:745-748. doi:10.1212/WNL.0000000000010652

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, characterized predominantly by respiratory symptoms, has affected a small subset of children. Neurologic manifestations have been described in adults, including encephalitis/meningitis, encephalopathy, strokes, seizures, and anosmia,[1,2] but there are few reports of neurologic manifestations in children with SARS-CoV-2.[3]

Multisystem inflammatory syndrome in children (MIS-C) has been reported in children following infection with SARS-CoV-2. MIS-C is characterized by a Kawasaki-like illness with persistent fever, elevated inflammatory markers, and multisystem organ involvement.[4] Although altered mental status has been described in the presence of MIS-C,[5] there are rare reports of severe encephalopathy or focal brain lesions in children with MIS-C.

We report a case of a 2-year-old with MIS-C presenting with altered mental status, who was found to have abnormal EEG and MRI findings.

Case

A previously healthy 33-month-old boy presented to the emergency department with 2 days of fever, emesis, and rash. Examination revealed a tachycardic, interactive toddler with erythematous macules on his thighs. Nasopharyngeal SARS-CoV-2 reverse transcription PCR testing was initially negative; the repeat test was indeterminate. SARS-CoV-2 antibody testing was positive. Laboratory findings were remarkable for normal white blood cell count with bandemia and elevated inflammatory markers. Chest radiograph was unremarkable. Cardiac markers were normal; echocardiogram showed trace pericardial effusion. Electrocardiogram demonstrated sinus tachycardia without improvement with fluid resuscitation. He was admitted to the hospital and treated with empiric antibiotic therapy for 48 hours, IV methylprednisolone, IV immunoglobulin (IVIG), anakinra, prophylactic anticoagulation, and supportive therapy for a presumed diagnosis of MIS-C. The figure depicts the patient's clinical course.

The patient developed worsening respiratory status over the subsequent 24–48 hours, requiring noninvasive respiratory support and diuresis. He was irritable, but alert and active. Chest radiograph displayed bilateral pleural effusions. Echocardiogram revealed decreased left ventricular systolic function. Laboratory findings demonstrated uptrending inflammatory and cardiac markers and thrombocytopenia. On hospital day 6, he became increasingly somnolent in the absence of sedative medication.

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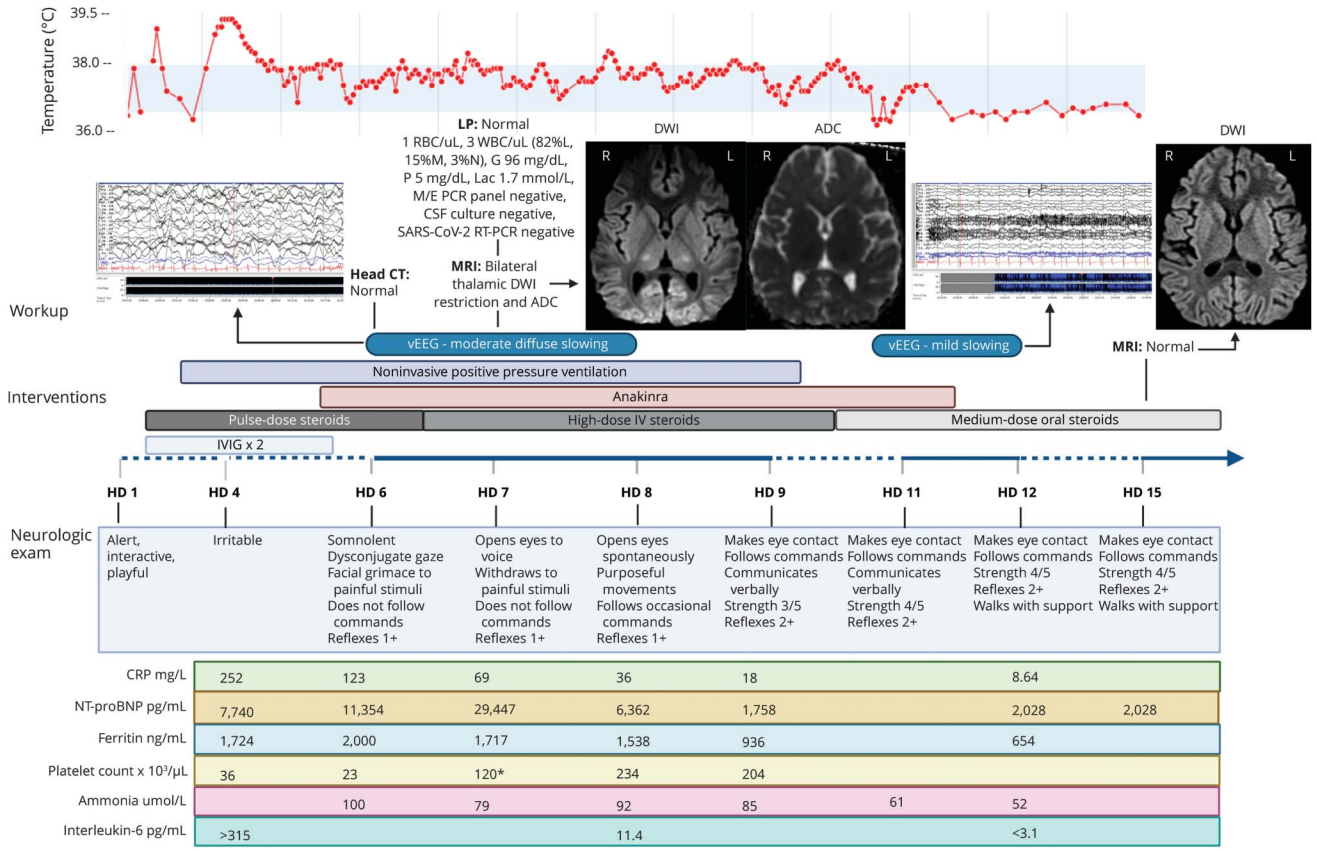
Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Figure Timeline of the patient's course



ADC = apparent diffusion coefficient; CRP = C-reactive protein; DWI = diffusion-weighted imaging; G = glucose; HD = hospital day; IVIG = IV immunoglobulin; L = lymphocytes, M = monocytes; Lac = lactic acid; LP = lumbar puncture; M/E = meningitis/encephalitis; N = neutrophils; NT-proBNP = N -terminal-pro-B-type natriuretic peptide; P = protein; pg/mL = picogram/milliliter; RBC = red blood cell; SARS-CoV-2 RT-PCR = severe acute respiratory syndrome coronavirus 2 reverse transcription PCR; WBC = white blood cell. *Postplatelet transfusion.

On neurology consultation, the patient was somnolent, with slight facial grimace to noxious stimuli, diffuse hypotonia, and significant weakness. No visual changes were noted. Metabolic workup was only notable for hyperammonemia, and hepatic function was normal. Noncontrast head CT was normal. Lumbar puncture was unremarkable, including negative SARS-CoV-2 PCR in CSF. EEG showed moderate background slowing.

The following day, he remained somnolent on bilevel positive airway pressure, although with slight improvement in mental status, noted by eye opening to voice and withdrawal from noxious stimuli. His EEG was unchanged. Brain MRI revealed restricted diffusion in the bilateral lateral thalamic nuclei without T2/fluid-attenuated inversion recovery changes.

The patient's neurologic status continued to improve, and his fevers were treated with antipyretics; no additional neuroprotective strategies were used. On hospital day 9, he was consistently following commands, communicating verbally, and regaining his motor function, although he remained weak. By day 12, he was walking with support. Repeat EEG showed only mild diffuse slowing, and repeat brain MRI on day 15 showed resolution of the thalamic lesions. Brain magnetic resonance angiography and magnetic resonance spectroscopy were also normal. He was discharged home on day 15 on oral steroids, with mild residual weakness requiring physical therapy. Follow-up brain imaging has not yet been obtained.

Discussion

We report a case of a previously healthy child who met the criteria for MIS-C and developed reversible encephalopathy with moderate EEG slowing and bilateral thalamic lesions, which improved with continued treatment of his inflammatory syndrome.

There was no identified etiology for the diffuse slowing on EEG and brain MRI findings, as the patient never received sedatives or antiseizure medications, had no diffuse hypoxic events, and metabolic derangement was solely notable for moderately elevated ammonia, without other laboratory data suggestive of liver failure or hepatic encephalopathy. Despite ongoing elevated ammonia, he clinically improved. EEG findings in adults with SARS-CoV-2 have included slowing

with a disorganized background and epileptiform discharges; however, most of these adults were receiving sedation and/or antiseizure medication.[6]

A multicenter study characterized neuroimaging findings in adults with SARS-CoV-2 and neurologic symptoms, finding ischemic infarcts in 31%, intracranial hemorrhage in 6%, and nonspecific T2/fluid-attenuated inversion recovery hyperintensity with restricted diffusion in a few patients.[7] None had distinct thalamic lesions. Bilateral thalamic lesions have been seen in children with encephalitis associated with respiratory and West Nile viruses[8]; however, thalamic lesions associated with SARS-CoV-2 infection are rare. There are case reports of COVID-19–associated acute necrotizing encephalopathy with characteristic bilateral thalamic hemorrhagic lesions,[9] but there was no evidence on susceptibility-weighted imaging to suggest a hemorrhagic component in this patient.

Although MIS-C affects multiple organ systems, we are unaware of other patients with associated encephalopathy, EEG slowing, and thalamic lesions. Some have posited that encephalopathy associated with SARS-CoV-2 infection may be attributable to direct CNS infection and have found increased levels of cytokines and antibodies against SARS-CoV-2 in affected patients' CSF.[10] We suggest that this patient's encephalopathy may reflect CNS effects of his marked systemic inflammatory response, rather than direct entry of the virus into the CNS, as the encephalopathy paralleled his increasing laboratory inflammation, and CSF SARS-CoV-2 PCR was negative. Encephalopathy has also been described in postviral autoimmune encephalitis after herpes virus infections.[11] The etiology of MIS-C is unclear, but it has been postulated that it arises from postinfectious, acquired immune activation.[12] MIS-C and Kawasaki disease have overlapping features, and current evidence suggests that patients with MIS-C have good outcomes after treatment with immunomodulatory therapies such as IVIG and corticosteroids.[13] The patient had elevated interleukin-6 at the onset of his encephalopathy, which downtrended as he clinically improved. If the patient's CNS manifestations reflect his systemic inflammatory response in the setting of MIS-C, this supports immune modulation as treatment, including corticosteroids, IVIG, and anakinra, as opposed to antiviral therapy.

Given the prevalence of SARS-CoV-2 and the growing numbers of children with MIS-C, it is imperative that we investigate the underlying etiology of associated neurologic manifestations and the appropriate therapies for these patients.

Acknowledgment

The authors thank the patient and his family, the physicians, nurses, medical assistants, and support staff involved in the care of this patient and the microbiology and core laboratory staff.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* June 16, 2020. Accepted in final form August 3, 2020.

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Min Ye Shen, MD	Columbia University Irving Medical Center, Department of Neurology; NewYork-Presbyterian Hospital; New York	Acquired and analyzed data and drafted and revised the manuscript
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Danielle K. McBrian, MD	Columbia University Irving Medical Center, Department of Neurology, Division of Child Neurology; NewYork-Presbyterian Hospital; New York	Acquired data
Kiran Thakur, MD	Columbia University Irving Medical Center, Department of Neurology; NewYork-Presbyterian Hospital; New York	Revised the manuscript

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Appendix *(continued)*

Name	Location	Contributions
Wendy Silver, MD, MA	Columbia University Irving Medical Center, Department of Neurology, Division of Child Neurology; NewYork-Presbyterian Hospital; New York	Interpreted data and revised the manuscript
Jennifer M. Bain, MD, PhD	Columbia University Irving Medical Center, Department of Neurology, Division of Child Neurology; NewYork-Presbyterian Hospital; New York	Designed and conceptualized the report; interpreted data; and revised the manuscript

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Neurology 2020;95;745-748 Published Online before print August 26, 2020
DOI 10.1212/WNL.0000000000010652