



# Multisystem Inflammatory Syndrome in Children Associated with Status Epilepticus

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A 12-year-old boy presented to the emergency department with findings concerning for multisystem inflammatory syndrome in children. After clinical stabilization following treatment with antibiotics, remdesivir, and anakinra, the patient was noted to have episodes of altered mentation. Video electroencephalogram revealed status epilepticus, which was subsequently controlled with antiepileptic medications. (*J Pediatr* 2020;227:300-1).

A 12-year-old boy with no prior medical problems presented to the emergency department with 4 days of fever up to 39.5°C and 2 days of worsening right-sided neck swelling. The patient reported trismus and loss of smell and taste, as well as difficulty swallowing. The patient's mother reported her own loss of smell several weeks before presentation. Physical examination was notable for dry, cracked lips, tender right-sided neck and jaw swelling, and bilateral conjunctival injection, as well as a blanching, macular abdominal rash. Fluid resuscitation improved his tachycardia and hypotension. Initial laboratory results demonstrated leukocytosis, thrombocytopenia, acute kidney injury, and elevated inflammatory markers (Table). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction from a nasopharyngeal swab sample was positive. Neck computerized tomography (CT) showed a retropharyngeal fluid collection. The patient was started on enoxaparin, vancomycin, ampicillin-sulbactam, and clindamycin.

During the initial hospitalization, the patient required supplemental oxygen and was transferred to the pediatric intensive care unit. Retropharyngeal exploration under anesthesia revealed no discrete abscess. Postoperatively, the patient failed extubation owing to acute respiratory failure, and was started on furosemide for fluid overload. On hospital day 3, the patient was given intravenous immunoglobulin (2 g/kg) for treatment of possible multisystem inflammatory syndrome in children (MIS-C), after which he became hypotensive and required an epinephrine infusion. On hospital day 6, remdesivir and anakinra were initiated, and antibiotics were narrowed to ampicillin-sulbactam. On hospital day 7, the patient was successfully extubated, and inflammatory markers began to decrease. The boy was weaned off epinephrine and furosemide infusions. He completed a 5-day course of remdesivir and continued to show improvement in laboratory findings. Serum SARS-CoV-2 Immunoglobulin G (IgG) sent on hospital day 9 was positive.

After extubation, the patient began to display brief, waxing and waning episodes of rapid, tangential speech, hyperactiv-

ity, and emotional lability while undergoing wean from sedation medications. Serial physical examinations identified no focal findings on neurologic examination. On hospital day 11, the patient developed an episode of altered mental status overnight, during which he became agitated and pulled out his arterial catheter. He had no memory of this event the following morning. The consulting neurologist recommended video electroencephalogram, which revealed 6 subclinical seizures over a 3-hour period ranging from 20 seconds to 8 minutes in duration. The patient was treated with a loading dose of levetiracetam. Over the next 24 hours, the patient had 12 additional seizures, 3 of which lasted for more than 10 minutes. The patient was given lorazepam and fosphenytoin with improvement in seizure frequency. He subsequently displayed a decreased level of consciousness with minimal responsiveness to commands. Video electroencephalogram indicated focal epilepsy arising in the central region with diffuse bifrontal spread and evidence for nonspecific cerebral dysfunction over the frontocentral region. Noncontrast head CT, magnetic resonance imaging, magnetic resonance angiogram, and magnetic resonance venogram were all unremarkable. Cerebrospinal fluid studies revealed normal cell counts, negative cultures and meningococcal panel, and negative SARS-CoV-2 polymerase chain reaction. Altered mental status resolved by hospital day 12 and video electroencephalogram was discontinued on hospital day 17 after titration of levetiracetam and oxcarbazepine. The patient remained at this baseline neurologic status until discharge on hospital day 26.

## Discussion

Although initial research suggested that severe illness and death are rarely seen in children with coronavirus disease-19 infection, there have been reports of children presenting with Kawasaki-like, systemic inflammatory responses in the

MIS-C      Multisystem inflammatory syndrome in children  
SARS-CoV-2      Severe acute respiratory syndrome coronavirus 2

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**Table. Laboratory data**

Laboratory markers (reference range)	Hospital day 1	Hospital day 6	Hospital days 10-11
Albumin (3.4-5.0 g/dL)	3.2	2.7	2.8
Brain natriuretic peptide (<100 pg/mL)	–	1067	–
Creatine kinase (29-168 U/L)	340	–	–
C-reactive protein (0-5 mg/L)	322	421.4	60.3
D-Dimer (<230 ng/mL)	632	816	458
Erythrocyte sedimentation rate (0-10 mm/h)	117	–	–
Ferritin (22-248 ng/mL)	633	569	508
Fibrinogen (150-450 mg/dL)	–	843	279
IL-6 (≤5 pg/mL)	176	–	–
Lactate dehydrogenase (125-220 U/L)	292	270	–
Platelets (10 <sup>3</sup> /μL)	109	207	421
Procalcitonin (ng/mL)	61.6	–	–
SARS-CoV-2 polymerase chain reaction (negative)	Positive	–	–
Troponin (<0.04 ng/mL)	0.01	0.11	–
White blood cells (3.8-9.8 10 <sup>3</sup> /μL)	18.3	28.1	4.6

weeks after acute infection with SARS-CoV-2, now referred to as MIS-C.<sup>1</sup> This evolving syndrome has been characterized by persistent fevers, elevated inflammatory laboratory markers, and single- or multiorgan dysfunction. We report MIS-C-associated status epilepticus, as defined by the Neurocritical Care Society criteria of 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery to baseline between seizures.<sup>2</sup>

Neurologic involvement during the acute phase of SARS-CoV-2 infection has been documented among adults, with widespread reports of headache, disturbed consciousness, loss of smell and taste, paresthesias, seizures, and stroke.<sup>3,4</sup> Prior studies of other severe coronavirus infections have also found central nervous system involvement, and following the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak, pathology reports of infected individuals identified signs of cerebral edema, meningeal vasodilation, neuronal ischemia, and demyelination, with monocytic and lymphocytic infiltration in brain vasculature.<sup>4,5</sup> SARS-CoV particles were also detected in brain tissue.<sup>4,5</sup>

Previous reports of MIS-C suggest a pattern of exposure to the novel coronavirus several weeks before the development of new, Kawasaki-like symptoms and increasing inflammatory markers. In this case, the history of loss of olfaction in the patient's mother several weeks before presentation suggests a similar timeline. Although the presence of SARS-CoV-2 IgG antibodies has been reported as early as 4 days after symptom onset, seroconversion more frequently occurs after the second week of infection.<sup>6</sup> This patient's seizure activity may, therefore, represent a complication of the hyperinflammatory response of MIS-C rather than acute coronavirus disease-19. However, the exact etiology of his seizures remains unknown given the inability to detect viral particles in cerebrospinal fluid, normal cell counts and protein in the cerebrospinal fluid, and the absence of gross findings of arteritis or other abnormalities on brain imaging.

Status epilepticus has not been identified with use of anakinra or remdesivir.

Other hyperinflammatory syndromes are known to manifest with severe neurologic findings. Neurologic involvement has been reported in hemophagocytic lymphohistiocytosis and macrophage activation syndrome, including seizures, stroke, myelopathy, altered consciousness, nerve palsies, and demyelination.<sup>7,8</sup> Kawasaki disease can rarely present with central nervous system findings, including decreased consciousness, seizures, and hemiplegia.<sup>9</sup> As an acute systemic vasculitis, some have speculated that cerebral hypoperfusion may play a role in these symptoms.

The current case illustrates the importance of recognizing potential central nervous system involvement during MIS-C. Clinicians treating affected patients should be highly attentive to subtle changes in clinical and mental status. Given the severity of illness in patients with MIS-C, acute changes in mental status may be masked by the use of sedating medications, and many of these patients are also at risk of delirium. Because of these confounding factors, it is even more critical that clinicians maintain a high index of suspicion for severe neurologic complications as we continue to investigate the underlying pathophysiology of this emerging clinical entity. ■

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