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ABSTRACT

Background: Acute ischemic stroke (AIS) is rare in children and diagnosis is often delayed. Neurological involvement may occur in multisystem inflammatory syndrome in children (MIS-C), but very few cases of AIS in patients with MIS-C have been reported. Case Descriptions: We report two cases of AIS presenting with large vessel occlusive (LVO) disease in previously healthy adolescents recently exposed to SARS-CoV-2 infection. Both patients were subsequently diagnosed with and treated for MIS-C. Here, we discuss the course of their treatments and clinical responses. Conclusion: Early recognition and diagnosis of LVO in children with MIS-C is critical in order to make available all treatment options to improve clinical outcomes.

INTRODUCTION:

The coronavirus disease 2019 (COVID-19) pandemic is a global health emergency caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has affected millions of people worldwide. Initially designated as a symptomatic disease in adults, a novel symptomatic syndrome in the pediatric population has emerged [1]. Multisystem inflammatory syndrome in children (MIS-C) is a condition seen only in children that is temporally related to either concurrent or recent SARS-CoV-2 exposure and/or infection, and can be associated with high morbidity and mortality.

While MIS-C most commonly presents with gastrointestinal, respiratory, and cardiac involvement, neurological involvement has been reported in 11-30% of patients [2,3]. Because acute ischemic stroke (AIS) is uncommon in pediatric patients, there can be a delay in diagnosis leading to high morbidity and mortality. Given the time-sensitive nature of AIS treatment, it is critical that
Clinicians are aware of the risk of stroke in MIS-C. Here, we report two cases of MIS-C-associated large vessel occlusive (LVO) AIS in previously healthy adolescents, and review the paucity of existing literature reporting similar cases.

**CASE 1:**
A previously healthy right-handed 15-year-old girl awoke with acute aphasia and right hemiparesis. She was last known to be in her normal state of health 10 hours prior to symptom recognition. She had no history of head trauma. One week prior, she had tested positive for SARS-CoV-2 following several days of fevers, headache, abdominal pain, and generalized weakness.

Initial National Institute of Health Stroke Scale (NIHSS) was 15. Computed tomography (CT), CT angiography (CTA) of the head and neck, and CT perfusion (CTP) demonstrated a small left insular hypodensity with a distal left middle cerebral artery (MCA) M2 branch occlusion (Figure 1A). She was transferred to our comprehensive stroke center for potential thrombectomy. On arrival, her symptoms had improved with complete resolution of deficits. Repeat arterial imaging demonstrated patent cerebral vasculature. She was admitted to our pediatric intensive care unit (PICU) for further evaluation and management.

Initial laboratories demonstrated leukocytosis, renal and cardiac dysfunction, and markedly elevated inflammatory markers. Transthoracic echocardiogram (TTE) with bubble study demonstrated a left ventricle ejection fraction (LVEF) of 45% with global strain and mild mitral valve regurgitation. Cardiac magnetic resonance imaging (MRI) showed small pericardial effusion. MRI brain with diffusion weighted imaging (MRI-DWI) showed scattered infarcts in the
left caudate, insula, and frontal operculum, and a restricted diffusion in the splenium of the corpus callosum; the latter lesion resolved on follow up studies (Figure 1B-D). Lower extremity doppler studies were negative for deep venous thrombosis (DVT).

The patient met CDC criteria for MIS-C based on her known recent SARS-Cov2 infection, multisystem involvement (renal, cardiac, neurologic), and elevated inflammatory markers [4]. She was treated with intravenous immunoglobulin (IVIG) 2g/kg and IV methylprednisolone 2mg/kg/day for five days, followed by a three-day oral prednisone taper, and therapeutic enoxaparin 1mg/kg twice daily for 3 months. A repeat TTE on day 6 showed improved LVEF. Upon discharge, she had subtle right hemiparesis with a Pediatric Stroke Outcome Measure (PSOM) of 1.5, which had completely resolved (PSOM 0) at 30-day follow up.

**CASE 2**

A previously healthy right-handed 16-year-old girl without any history of head trauma was found obtunded and non-verbal after three days of fevers, nausea, vomiting, and diarrhea. Her family had been ill with SARS-CoV-2 about a month prior.

Upon arrival, her blood pressure was 70/40 requiring vasopressor support. CT head showed a subtle left insular hypodensity. An initial suspicion of bacterial meningoencephalitis warranted lumbar puncture and initiation of antibiotic treatment. Five hours after initial presentation, she developed right-sided hemiparesis (NIHSS 16). An urgent CTA head and neck showed left internal carotid artery (ICA) terminus occlusion (Figure 1E), with unfavorable CTP study. She was
transferred to our institution’s PICU for escalation of care, where she was intubated for airway protection.

Initial laboratories showed leukocytosis, renal and cardiac dysfunction, elevated inflammatory markers and positive SARS-CoV-2 IgG serology. TTE demonstrated a LVEF of 35% which improved after 12 hours. An apical thrombus was confirmed on cardiac MRI and she was started on anticoagulation with heparin drip. Several subacute infarcts were noted on MRI-DWI brain in the left insula, caudate, frontal and temporal lobes (Figure 1F, 1G), in addition to diffusion restriction with corresponding aDC changes involving the splenium of the corpus (Figure 1F, 1G); the latter resolved on follow up studies five days later (Figure 1H).

She was diagnosed with MIS-C based on the CDC criteria [4] and was treated with a single dose of IVIG 2g/kg and IV methylprednisolone 1mg/kg/day for 5 days followed by a three-day oral prednisone taper. Her hospitalization was complicated by a catheter-associated right lower extremity DVT. Heparin drip was transitioned to enoxaparin 1mg/kg twice daily and aspirin 81 mg daily. Throughout her hospital stay, she made gradual improvement with speech and mobility. She was ultimately discharged to an acute rehabilitation facility with PSOM of 3. On day 41 outpatient follow up, she was independent in all activities of daily living with mild expressive aphasia and trace right hemiparesis with PSOM of 2.
DISCUSSION

The COVID-19 pandemic has impacted millions of people globally. Over 4 million children have tested positive for SARS-CoV-2 thus far in the United States [5]. COVID-19 in children is associated with MIS-C, a debilitating multisystem syndrome that can present in children weeks after exposure to SARS-CoV-2. We report two cases of AIS due to LVO in previously healthy adolescents with MIS-C. These two cases illustrate the diverse neurological presentations of COVID-19 in children, specifically coagulopathy associated with this infection.

The pathophysiology linking MIS-C to AIS is not fully understood, although emerging data from adult COVID-19-associated AIS suggest a combination of etiologies. These include venous stasis, hyper-viscosity in critically ill patients, viral endothelial injury leading to hypercoagulability, and myocardial involvement causing reduced LVEF and subsequent cardioembolism. In adults, the connection between SARS-CoV-2 and inflammation has been proposed to involve compromise of vascular integrity activating the clotting cascade, triggering platelet reactivity, cytokine storm, and immune complexes that contribute to the formation of thromboses [1,6]. In children, especially those with delayed MIS-C relative to initial infection, a delayed immune-mediated inflammatory response stimulated by macrophages, neutrophils, and monocytes followed by the production of antibodies from plasma and B-cells, appears to be a more likely pathogenesis than direct viral invasion of tissues.

In a comprehensive study of MIS-C spanning 53 pediatric health centers across the US, Feldstein et al. reported that among adolescents aged 13-20 years, the gastrointestinal, respiratory, and
cardiac systems were the most commonly affected at 90%, 87%, and 80%, respectively [2]. Neurological involvement has been reported in 11-30% of children with MIS-C [2,3]. Commonly reported neurological symptoms include fatigue, generalized weakness, confusion, headache, and loss of sense of taste or smell [7]. More severe neurologic manifestations such as seizures, encephalopathy, and cerebral edema were uncommon [7].

AIS due to LVO in children is exceedingly rare. Even in the setting of COVID-19 and MIS-C, very few cases of AIS have been reported. Beslow et al. surveyed 42 centers and found 8 AIS in 971 (0.82%) pediatric patients with SARS-CoV-2, four of which were with LVO [8]. Transient involvement of the splenium of the corpus callosum was seen in both our patients, which has been reported to be associated with various central nervous system infections including SARS-CoV-2 [9]. The current literature includes nine other published cases of pediatric LVO AIS in the setting of COVID-19 (Table 1) [8, 10-13] Including our two cases, the ages range from 8 to 16 years, some of which were initially asymptomatic with positive PCR or IgG serology. Interestingly, though all patients had recent or proven concurrent SARS-CoV-2 infection, only three other reported patients met full diagnostic criteria for MIS-C [8,10]. Both of our patients and the patient reported by Tiwari with LVO AIS and MIS-C were successfully treated with IVIG, steroids, and anticoagulation; the treatment for the two MIS-C cases reported by Beslow was not specified [8,10].

Medical management of MIS-C is largely based on established treatments for Kawasaki disease including IVIG, aspirin, and corticosteroids [1]. While emerging data suggest improved cardiovascular function in patients with MIS-C initially treated with IVIG plus glucocorticoids
compared to IVIG alone [14], other studies show no difference in recovery from MIS-C after IVIG alone, IVIG plus glucocorticoids, and glucocorticoids alone [15]. Nevertheless, IVIG remains a mainstay for MIS-C treatment. Historically, IVIG has been associated with a potential increased risk of thromboembolic events including stroke, raising concerns for IVIG exacerbating a pro-thrombotic state due to MIS-C, especially in patients with AIS [16]. In Case 1, IVIG was administered according to published guidelines [1]; Case 2 was hematologically complex as she exhibited a larger AIS, and additional signs of hypercoagulability, including lower extremity DVT and left ventricular thrombus, which warranted discontinuing IVIG and treatment with low molecular weight heparin.

**CONCLUSION**

Pediatric AIS remains an infrequent complication of SARS-CoV-2. The two presented cases demonstrate an association between MIS-C and AIS due to LVO, thus expanding the literature on this rare condition. These cases illustrate the importance of early symptom recognition, timely diagnosis, and rapid intervention to improve clinical outcomes.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Vessel Distribution</th>
<th>COVID</th>
<th>MIS-C criteria met?</th>
<th>Organ Involvement</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE 1</td>
<td>15, F</td>
<td>L. MCA</td>
<td>+ PCR 1 wk prior + serology</td>
<td>Yes</td>
<td>Cardiac, renal</td>
<td>IVIG, methylprednisolone, prednisone, enoxaparin</td>
</tr>
<tr>
<td>CASE 2</td>
<td>16, F</td>
<td>L. ICA</td>
<td>+ serology only</td>
<td>Yes</td>
<td>Cardiac, renal, GI</td>
<td>IVIG, methylprednisolone, prednisone, enoxaparin, aspirin</td>
</tr>
<tr>
<td>Tiwari [10]</td>
<td>9, F</td>
<td>R. MCA</td>
<td>+ PCR At presentation</td>
<td>Yes</td>
<td>Cardiac</td>
<td>IVIG, methylprednisolone, dexamethasone, remdesivir, LMWH</td>
</tr>
<tr>
<td>Beslow (1)</td>
<td>10, M</td>
<td>R. MCA + cerebellar infarcts</td>
<td>+ PCR 1 wk prior + serology</td>
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<td>Not specified</td>
<td>Not specified</td>
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<tr>
<td>Beslow (2)</td>
<td>14, M</td>
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<td>+ PCR 1 wk post stroke</td>
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<td>Respiratory, GI</td>
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<tr>
<td>Beslow (3)</td>
<td>10, M</td>
<td>B. PCA</td>
<td>+ PCR 1 wk post stroke</td>
<td>No</td>
<td>Respiratory</td>
<td>Not specified</td>
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<td>Beslow (4)</td>
<td>16, M</td>
<td>L. MCA + B. ACA</td>
<td>+ PCR 1 wk prior</td>
<td>No</td>
<td>Not specified</td>
<td>Not specified</td>
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<tr>
<td>Appavu (1)</td>
<td>8, F</td>
<td>B. MCA</td>
<td>+ PCR 3 weeks prior + serology</td>
<td>No</td>
<td>None</td>
<td>Thrombectomy</td>
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<tr>
<td>Appavu (2)</td>
<td>16, M</td>
<td>L. MCA</td>
<td>+ PCR 4 weeks prior</td>
<td>No</td>
<td>Cardiac, renal</td>
<td>Enoxaparin only</td>
</tr>
<tr>
<td>Gulko [12]</td>
<td>13, F</td>
<td>L. MCA</td>
<td>+ PCR At presentation</td>
<td>No</td>
<td>None</td>
<td>Not specified</td>
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<tr>
<td>Mirzaee [13]</td>
<td>12, M</td>
<td>L. MCA</td>
<td>+ PCR At presentation</td>
<td>No</td>
<td>None</td>
<td>“conservative”</td>
</tr>
</tbody>
</table>

R= right; L= Left; B= bilateral; MCA= middle cerebral artery; ICA= internal carotid artery; ACA = anterior cerebral artery; PCA= posterior cerebral artery; PCR= polymerase chain reaction; IVIG= intravenous immunoglobulin; LMWH = low molecular weight heparin
REFERENCES


FIGURE 1:

Case 1: Axial imaging with CTA maximum intensity projection demonstrating occlusion of the distal M2 branch of the left MCA (A), MRI diffusion weighted imaging (DWI) showing restricted diffusion in the insular ribbon, caudate head and splenium of the corpus callosum (B) with corresponding aDC changes (C) and resolution of the splenial lesion on T2 FLAIR on repeat imaging (D). Case 2: Axial imaging with CTA maximum intensity projection demonstrating occlusion of the left ICA terminus (E), MRI DWI shows restricted diffusion in the left MCA territory and splenium of the corpus callosum (F) with corresponding aDC changes (G), and resolution of the splenial lesion on T2 FLAIR on repeat imaging (H).

CTA: computerized axial tomography; DWI: diffusion weighted imaging; MCA: middle cerebral artery; aDC: apparent diffusion coefficient; FLAIR: fluid attenuation inversion recovery; ICA: internal carotid artery
No author has any competing interests or disclosures.