Arteritis and Large Vessel Occlusive Strokes in Children After COVID-19 Infection

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We describe 2 previously healthy children who suffered disabling arterial ischemic strokes because of acute intracranial large vessel occlusion within 3 to 4 weeks of coronavirus disease 2019 (COVID-19) infection. Both children presented from communities with high COVID-19 case rates in the Southwest United States. An 8-year-old American Indian girl experienced severe iron deficiency anemia requiring blood transfusion and presented with bilateral middle cerebral artery (MCA) distribution strokes 3 weeks later. She underwent emergent mechanical thrombectomy of the left MCA with successful clot retrieval but experienced reocclusion of that artery 5 hours after intervention. She also had evidence of cerebral arteritis on catheter angiography and vessel wall imaging, and clot pathology revealed recently formed, unorganized platelet- and fibrin-rich thrombus with sparse clusters of erythrocytes, degenerated histiocytes, few eosinophils, and rare neutrophils. A 16-year old African American boy demonstrated evidence of arteritis on brain magnetic resonance angiography and serological markers of cardiac and renal injury accompanied by positive lupus anticoagulant antibodies. The children described in this report express clinical features inconsistent with focal cerebral arteriopathy, including elevated markers of systemic inflammation in both bilateral MCA strokes in one case and multiple organ system dysfunction in the other case. Neither patient fulfilled criteria for multisystem inflammatory syndrome in children, given absence of fever. These cases illustrate that systemic postinfectious arteritis with cerebrovascular involvement may complicate COVID-19 infection in previously healthy school-aged children, and their presentations may overlap but not fulfill criteria for multisystem inflammatory syndrome in children or focal cerebral arteriopathy.

Coronavirus disease 2019 (COVID-19) has been revealed to cause a wide range of neurologic manifestations, including stroke. The incidence of cerebrovascular involvement in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported between 2% and 6%.1 Although the annual incidence rates of pediatric arterial ischemic stroke (AIS) range from 1.3 to 1.72 cases per 100 000 children in Europe and North America,2 little is known about the occurrence of AIS in pediatric COVID-19.3 In this report, we describe 2 previously healthy children who suffered disabling AIS because of acute intracranial large vessel occlusion (LVO) within 3 to 4 weeks of COVID-19 infection. Both children presented from communities with high COVID-19 case rates in the Southwest United States.
Clinical and imaging features suggesting postinfectious systemic inflammatory arteritis complicated by central nervous system (CNS) involvement are discussed. These patients carried clinical presentations that overlapped but did not fulfill criteria for multisystem inflammatory syndrome in children (MIS-C) or focal cerebral arteriopathy (FCA).

**CASE 1**

An 8-year-old American Indian girl presented with new onset right hemiplegia and language impairment. She was assessed to have a National Institutes of Health Stroke Scale (NIHSS) score of 15. The NIHSS score was used in lieu of the pediatric NIHSS score because not all clinicians involved in the patient’s care were familiar with the pediatric NIHSS score. Three weeks before stroke onset, the patient experienced an acute febrile illness symptomatic with mild cough. Two weeks later, she received a blood transfusion for newly discovered iron deficiency anemia (hemoglobin level of 2.8 g/dL) by using donor blood screened negative for COVID-19 antibodies. Brain MRI performed within 10 hours of last known well revealed small completed infarctions in the middle cerebral artery (MCA) territories bilaterally. Brain magnetic resonance angiography (MRA) revealed proximal left M1 occlusion. A nasopharyngeal COVID-19 polymerase chain reaction (PCR) test result was negative. Emergent mechanical thrombectomy by stent-retriever-assisted contact aspiration resulted in reperfusion of the proximal MCA vasculature. Catheter angiography revealed arteriopathic changes in recanalized distal MCA branches (Fig 1). Follow-up brain MRI and MRA performed 5 hours after thrombectomy revealed reocclusion of the distal left M1 and cortical extension of infarction into part of the MCA territory. Magnetic resonance (MR) vessel wall imaging (VWI) revealed concentric mural enhancement of the left internal carotid artery (LICA) consistent with inflammatory intracranial arteriopathy (Fig 2A). Bubble echocardiography study, 12-lead electrocardiogram, and troponin levels were normal. Laboratory studies were significant for positive qualitative COVID-19 immunoglobulin G as well as a constellation of elevated inflammatory marker levels (D-dimer [1.83 μg/mL fibrinogen equivalent unit], serum interleukin 6 [3.2 pg/mL], C-reactive protein [2.7 mg/dL], and white blood cell count [14 800 cells per mm³]). Clinical symptoms did not fulfill criteria for MIS-C, given absence of fever. Histopathological examination of the thrombectomy specimen revealed recently formed, unorganized platelet- and fibrin-rich thrombus with sparse clusters of erythrocytes, degenerated histiocytes, few eosinophils, and rare neutrophils. No endothelial cells, smooth muscle cells, collagen, or elastic tissue fibers were detected (Fig 3). The patient was anticoagulated for 5 days, then transitioned to single agent antiplatelet therapy with aspirin. She was transferred to acute inpatient rehabilitation on poststroke day 5.
A 3-day course of intravenous Solumedrol was started on poststroke day 6. NIHSS remained 15 on poststroke day 7. The patient underwent a total of 26 days of inpatient rehabilitation and was discharged from the hospital on aspirin 81 mg daily. After discharge, she had persistent mixed receptive-expressive aphasia and dysarthria but demonstrated improvement through the rehabilitation process. She was discharged with a Modified Rankin Scale score of 4, possessing the ability to ambulate with a walker and minimal assistance for activities of daily living.

**CASE 2**

A 16-year-old African American boy presented 7 days after his last known well with dense right hemiparesis and global aphasia (NIHSS 19). The NIHSS score was used because not all clinicians involved in the patient’s care were familiar with the pediatric NIHSS score. Brain MRI and MRA revealed a complete left MCA territory infarction, irregularity of left M1 (suggestive of arteritis), and occlusion of left MCA bifurcation (Fig 2B). A nasopharyngeal COVID-19 PCR test result was negative, although the patient had been symptomatic with fever and cough and tested positive with nasopharyngeal COVID-19 PCR 30 days before presentation with interim improvement of symptoms. Seven days before admission, he became progressively lethargic, and 3 days before, he was noted to be limping by his mother, who brought him in for decreased responsiveness. On admission, he had an elevated troponin level (0.782 ng/mL) and a prolonged PR interval (207 milliseconds) on electrocardiogram with a normal echocardiogram. He was also noted to have elevation in the creatinine level (5.2 mg/dL) and inflammatory marker levels (erythrocyte sedimentation rate 59 mm/hour, C-reactive protein 13.6 mg/dL, ferritin 468 ng/mL), but he did not meet criteria for MIS-C because of absence of fever. Serology was also notable for an elevated D-dimer level (6.06 µg/mL), fibrinogen level (680 mg/dL), and factor VIII activity (>297%) as well as positive lupus anticoagulant antibodies. MR VWI obtained 2 weeks after clinical presentation did not reveal mural enhancement. The patient was anticoagulated on a therapeutic heparin infusion. The NIHSS score was 15 on day 3. The patient acutely decompensated on day 4 with new onset left-sided weakness and increased work of breathing. He was intubated and transferred to the ICU, with repeat computed tomography of the head and MRI of the brain revealing worsening edema and increased midline shift. He was monitored in the ICU and had improvement of left-sided symptoms overnight. He was transitioned to therapeutic Lovenox once his creatinine normalized and transferred out of the ICU on hospital day 7. His NIHSS was 7 on hospital day 16, and he was transferred to inpatient rehabilitation. Outpatient follow-up 2 months after the index stroke revealed persistent dysarthria, aphasia, right facial palsy, and right upper extremity weakness with a Modified Rankin Scale score of 3.

**DISCUSSION**

Oxley et al recently described AIS from LVO as a presenting manifestation of COVID-19 in 5 young adult patients, with 2 of 5 patients having no preexisting medical comorbidities. The youngest, previously healthy patient reported to experience LVO stroke after acquiring COVID-19 infection in that series was 33 years old. Our report provides descriptions of previously healthy children presenting with AIS due to intracranial LVO after COVID-19 infection. Although most reports indicate that the majority of healthy children with COVID-19 infection experience only mild symptoms, emerging data suggest that some will develop a life-threatening illness referred to as MIS-C, a delayed hyperinflammatory syndrome with median onset of 25 days after COVID-19 symptom onset. Although multisystem organ failure has been described in children with MIS-C, LVO stroke has not been previously reported as a manifestation.

Each of the 2 patients reported here suffered intracranial LVO stroke within 3 to 4 weeks of COVID-19 infection. One child demonstrated...
Evidence of arteritis on brain MRA with laboratory evidence of cardiac and renal injury accompanied by elevated markers of systemic autoimmunity. The other child with bilateral MCA distribution strokes had evidence of cerebral arteritis on catheter angiography and VWI. Postinfectious cerebral arteritis causing childhood LVO stroke is known to occur in the setting of numerous viral infections. The characteristic pattern has been described as FCA with variable unilateral involvement of the intracranial internal carotid artery, M1, or A1 in the absence of systemic disease. One case of FCA was recently described in a child found to have SARS-CoV-2 in nasopharyngeal and cerebrospinal fluid samples. The children described in this report express clinical features that are inconsistent with FCA, including elevated markers of systemic inflammation in both patients, bilateral MCA strokes in the patient in case 1, and multiple organ system dysfunction in the patient in case 2. Also noteworthy is that neither patient fulfilled criteria of MIS-C, given the absence of fever.

A broad spectrum of complications related to vascular inflammation, including AIS, is reported in COVID-19 patients with a number of proposed biological mechanisms. Entry of SARS-CoV-2 into host cells is mediated by binding of the virus to angiotensin-converting enzyme 2 receptors found on multiple sites, including vascular endothelial, neuronal, pulmonary, cardiac, and renal tissue. Laboratory studies of coronavirus-infected transgenic mice that express human angiotensin-converting enzyme 2 receptors have revealed a multiple organ system lymphohelic inflammatory process that features CNS vasculitis. Postmortem findings of viral inclusions within vascular endothelial cells and associated accumulation of inflammatory cells have led to a hypothesis that direct viral-induced endothelial inflammation is another mechanism of organ dysfunction and hypercoagulability in patients with COVID-19. Separately, there may be a postinfectious inflammatory phenomenon that is not a result of acute viral infection, but rather is secondary to immunoglobulin G antibody–mediated autoimmunity, which is the proposed mechanism for MIS-C. This may have represented the mechanism by which our patients developed AIS, given their time line of presentation 3 to 4 weeks after SARS-CoV-2 infection with negative PCR test results on admission and laboratory evidence of systemic inflammation.

The findings described in this report reveal that systemic postinfectious arteritis with CNS vascular involvement may complicate COVID-19 infection in previously healthy school-aged children. The arteritis seems to have a symptomatic prodromal phase and may lead to disabling and life-threatening LVO strokes. Clinical presentation may overlap but not fulfill criteria for MIS-C or FCA. Pediatric health care providers should be aware of this COVID-19 complication. Awareness of this entity may facilitate early diagnosis and treatment of affected children. Pediatric patients experiencing stroke generally suffer from diagnostic delays. Prompt recognition of stroke symptoms and early initiation of treatment have been associated with improved clinical outcomes.

**ABBREVIATIONS**

AIS: arterial ischemic stroke  
CNS: central nervous system  
COVID-19: coronavirus disease 2019  
FCA: focal cerebral arteriopathy  
LICA: left internal carotid artery  
LVO: large vessel occlusion  
MCA: middle cerebral artery  
MIS-C: multisystem inflammatory syndrome in children  
MR: magnetic resonance  
MRA: magnetic resonance angiography  
NIHSS: National Institutes of Health Stroke Scale  
PCR: polymerase chain reaction  
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2  
VWI: vessel wall imaging

**REFERENCES**


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