

Cerebral vasculopathy and strokes in a child with COVID-19 antibodies: illustrative case

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BACKGROUND The ability of coronavirus disease 2019 (COVID-19) to cause neurological insults in afflicted adults is becoming increasingly understood by way of an ever-growing amount of international data. By contrast, the pandemic illness's neurological effects in the pediatric population are both poorly understood and sparsely reported.

OBSERVATIONS In this case, the authors reported their experience with a preschool-age child with hydrocephalus who suffered multiterritory strokes presumed secondary to immune-mediated cerebral vasculopathy as a result of asymptomatic COVID-19 infection.

LESSONS Growing evidence indicates that COVID-19 can cause neurological sequelae such as encephalitis and strokes. In this case report, the authors discussed a case of cerebral vasculopathy and strokes in a pediatric patient who was positive for COVID-19.

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KEYWORDS COVID-19; stroke; cerebral vasculopathy; pediatric

A growing body of evidence indicates an association between coronavirus disease 2019 (COVID-19)—the pandemic illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)—and cerebrovascular disease. Since the emergence of the disease in December 2019, several case series have described an observed predilection for thrombogenicity,¹ vasculopathy,² and strokes,³ primarily in adult patients with COVID-19. In fact, studies have overwhelmingly found advanced age to be an independent increased risk factor for COVID-19–related stroke (CoV-S). The possible neurological consequences of infection in the pediatric population are comparatively underreported and, thus, less understood. We present a case of arteriopathy and multifocal CoV-S in a 4-year-old boy with a congenital cerebral ventricular malformation.

Illustrative Case

The patient is a 4-year-old boy who presented to our institution accompanied by his mother. He had been reporting headaches, which were associated with several bouts of vomiting followed by a tonic-clonic

seizure, for the preceding 2 days. To further evaluate his symptoms, non-contrast computed tomography (CT) of the brain was performed and showed subacute hydrocephalus. Of note, the patient tested positive for COVID-19 on routine admission testing but was asymptomatic.

An external ventricular drain (EVD) was placed for monitoring and relief of hydrocephalus. Postoperatively, the patient was awake and alert, with a stable neurological examination. An immediate postprocedural noncontrast CT demonstrated satisfactory catheter placement with interval reduction in ventriculomegaly. Magnetic resonance imaging (MRI) of the brain later demonstrated the membrane obstructing the right foramen of Monro, which was thought to be a congenital malformation and the cause of the child's hydrocephalus (Fig. 1). Magnetic resonance venography and cervical spine MRI the following day were without pathology.

Two days later (i.e., hospital day 3), the patient developed a new left-sided hemiparesis. Repeat MRI and magnetic resonance angiography (MRA) of the brain were performed because of the new

ABBREVIATIONS COVID-19 = coronavirus disease 2019; CoV-S = COVID-19–related stroke; CSF = cerebrospinal fluid; CT = computed tomography; EVD = external ventricular drain; IgG = immunoglobulin G; IL = interleukin; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PAI-1 = plasminogen activator inhibitor type 1; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

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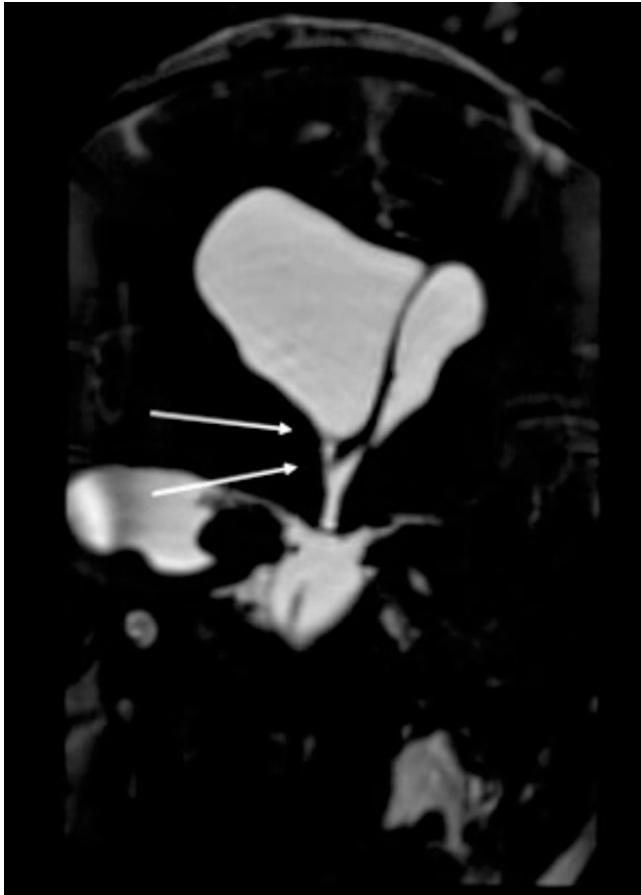


FIG. 1. MRI of brain, coronal fast imaging employing steady-state acquisition image. There are two axially coursing membranes covering the right foramen of Monro (arrows) and blocking outflow of the right lateral ventricle, causing hydrocephalus.

symptoms. The MRI showed new diffusion restriction indicative of infarctions throughout both hemispheres, thalami, and basal ganglia. These new findings were not present on the first MRI performed after the EVD was placed. MRA showed variable degrees of focal narrowing and irregularity along the courses of the distal left carotid artery, left M1 and M2 and right postbifurcation M1 segments of the middle cerebral arteries, right A1 segment of anterior cerebral artery, and left P2 and right P1 segments of the posterior cerebral arteries (Fig. 2). These findings were concerning for vasculitis or vasospasm.

Based on these findings, a stroke workup was initiated. Echocardiography confirmed a structurally and functionally normal heart with no evidence of emboli. The extensive coagulopathy workup that followed likewise produced mostly normal results, including D-dimer levels (Table 1). The boy's protein S level was mildly low, and he was discovered to be homozygous 4G/4G for the plasminogen activator inhibitor type 1 (PAI-1) gene. A battery of cerebrospinal fluid (CSF) infectious studies was ordered, including those for infections with known relationships to strokes, such as varicella zoster virus, herpes simplex viruses 1, 2, and 6, *Haemophilus influenzae*, and *Neisseria meningitidis*.⁴ All of these tests returned negative results, and all six of the patient's CSF cultures remained sterile (Table 1).

As previously discussed, the patient tested positive for COVID-19 after admission to the hospital but was asymptomatic. He tested

positive for SARS-CoV-2 immunoglobulin G (IgG) antibodies on blood testing as well as for the virus by polymerase chain reaction (PCR) testing on four separate serum samples during his hospitalization. However, he had no fever and no reported respiratory symptoms at home or on presentation to the hospital. Although the patient's CSF was negative for SARS-CoV-2 by PCR analysis, it was found to have significantly elevated levels of proinflammatory cytokines, predominantly interleukin (IL)-6 and IL-8 (Table 1). Empirical treatment with exogenous steroids was initiated for provoked vasculitis. He did not have additional infarcts after initiation of this treatment, as confirmed by surveillance MRI.

Intracranial pressure monitoring with an EVD was reliable throughout this time with patent external CSF diversion. After the patient's treatment for provoked vasculitis, he was taken to the neurosurgical operating room for ventricular endoscopy, which identified a membranous obstruction at the right foramen of Monro as the etiology of his subacute hydrocephalus. This membrane was opened, and a septum pellucidotomy was performed to place the previously segregated lateral ventricles into continuity and allow for CSF flow normalization. There were no surgical complications. External CSF drainage was continued postoperatively until his drain was successfully weaned and removed.

Routine surveillance MRI/MRA acquired after initiation of empirical treatment with high-dose steroids confirmed interval resolution of the patient's vascular findings without further infarcts.

Discussion

Observations

Current literature suggests that infections from COVID-19 are less prevalent in the pediatric population, with international retrospective data showing that children younger than 18 years constitute just 1% to 2% of all reported COVID-19 cases.² In one multicenter Italian study, of the 168 COVID-19–positive pediatric cases reported, none resulted in mortality or long-term morbidity.⁵ Stroke is also much less common in children compared to adults, but this highly morbid condition still affects approximately 2,500 children each year in the United States.⁶

In this case, the child presented with hydrocephalus due to a congenital blockage of the foramen of Monro. He was treated for hydrocephalus and remained neurologically stable postoperatively, and an initial MRI did not show significant infarcts. Incidentally, he was also found to be positive for COVID-19 on routine testing (unrelated to his hydrocephalus). Later, he showed clinical and MRI evidence of arteriopathy and new strokes, believed to be related to his COVID-19 diagnosis. His treated hydrocephalus seemed to be unrelated to his development of significant infarcts.

Recently, there has been increased focus on what appears to be an association between severe COVID-19 infections and cerebrovascular disease, including stroke^{3,7,8} and vasculitides,^{2,9} even in historically less susceptible demographics.^{10,11} One recent synthesis of available epidemiological data reported neurological COVID-19 manifestations in 901 patients across all studies.¹² Early data from New York City described ischemic infarcts in 32 patients with COVID-19 (0.9%).⁸ Another case series reported CoV-S in 5 relatively young patients who ranged in age from 33 to 49 years old.¹³ The incidence of CoV-S in the pediatric population is unclear but ostensibly far rarer. To our knowledge, only a small number of cases involving cerebral arteriopathy and stroke in this patient demographic has been published.^{4,14–17}

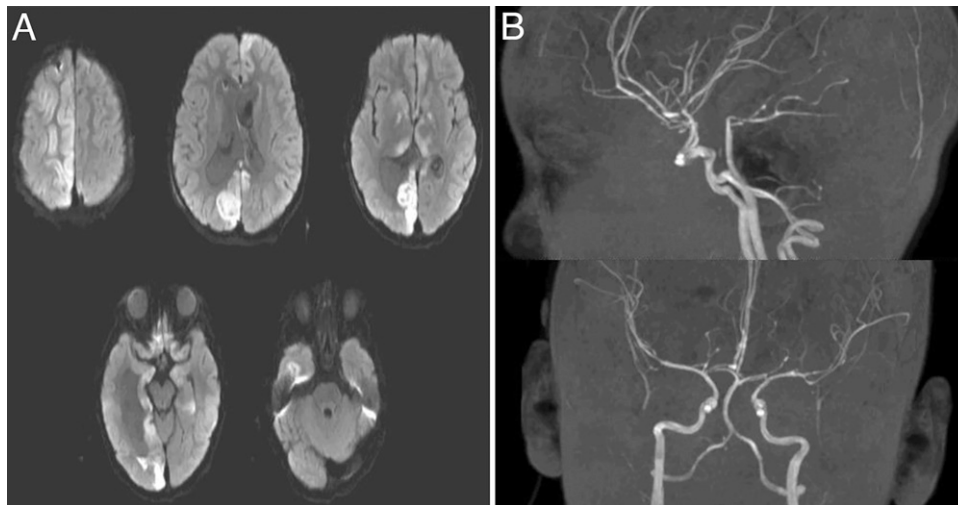


FIG. 2. A: MRI of brain, diffusion-weighted sequences. Axial images show new diffusion restriction indicative of cytotoxic edema secondary to infarction throughout both hemispheres, thalami, and basal ganglia. **B:** Lateral (*top*) and anteroposterior (*bottom*) images of MRA, three-dimensional maximum intensity projection images. Variable degrees of focal narrowing and irregularity are noted along the courses of the distal left carotid artery, left M1 and M2 and right postbifurcation M1 segments of the middle cerebral arteries, right A1 segment of anterior cerebral artery, and left P2 and right P1 segments of the posterior cerebral arteries.

Several theories exist regarding the pathophysiology of SARS-CoV-2's invasion of and damage to the nervous system. Leading theories on its effects on the nervous system include direct angiotensin-converting enzyme 2-mediated translocation into neural tissue, retroaxonal

transport via peripheral nerves in the respiratory or gastrointestinal systems, and direct hematogenous spread after systemic cytokine release and proinflammatory "priming" of these otherwise immune-privileged tissues.^{11,18,19} Expert opinion suggests that neurological injuries may

TABLE 1. Laboratory work-up

Thrombophilia Work-Up		CSF PCR Analysis for Infection		CSF Proinflammatory Marker Testing	
Test	Result	Infectious Agent	Result	Cytokine	Result
Anticardiolipin antibodies	IgA <11, IgG <14, IgM <12	<i>Escherichia coli K1</i>	—	IL-1 beta	<5
Antithrombin III	115	<i>Haemophilus influenzae</i>	—	IL-2	2 (H)
Beta-2 glycoprotein antibodies	<9	<i>Listeria monocytogenes</i>	—	IL-4	11(H)
D-dimer	0.49	<i>Neisseria meningitidis</i>	—	IL-5	2
Factor V Leiden	—	<i>Streptococcus agalactiae</i>	—	IL-6	338 (H)
Factor VIII level	106	<i>Streptococcus pneumoniae</i>	—	IL-8	250 (H)
Factor IX level	95	Cytomegalovirus	—	IL-10	3 (H)
Factor XI level	99	Enterovirus	—	IFN gamma	2
Homocysteine	2.5	Herpes simplex virus-1	—	TNF alpha	1
Lipoprotein (a)	27	Herpes simplex virus-2	—	GM-CSF	2 (H)
Lupus anticoagulant	—	Herpes simplex virus-6	—		
PAI-1	4G/4G	Human parechovirus	—		
Phosphatidylserine antibodies	IgA <20, IgG <10, IgM <25	Varicella zoster virus	—		
Protein C level	80	Epstein-Barr virus	—		
Protein C function	90	<i>Cryptococcus neoformans/gattii</i>	—		
Protein S level	32 free (low), 70 total	SARS-CoV-2	—		
Protein S function	42				
Prothrombin gene mutation	—				

GM-CSF = granulocyte-macrophage colony-stimulating factor; H = high; IFN = interferon; TNF = tumor necrosis factor; — = not detected.

then arise from any permutation of direct tissue damage, autoimmune-mediated postviral syndrome, or systemic comorbidities secondary to critical illness, such as metabolic derangement or hypercoagulability.^{8,20}

A predilection for arterial and venous thrombosis with COVID-19 infection has been described. A study on patients with COVID-19 in two Dutch intensive care units reported a 31% rate of thromboembolic events. Sepsis-induced inflammation and resultantly high circulating levels of D-dimer have been identified as the most likely source of this phenomenon.^{3,8,21} However, our patient's D-dimer levels were within normal limits. Consideration was given to the PAI-1 4G/4G homozygosity discovered in our patient as a possible thromboembolic risk factor, but current research indicates that the 4G allele is associated with a decreased, not increased, risk of stroke.^{22,23} Previously published data have implicated anticardiolipin A, lupus anticoagulant, and B2-glycoprotein antibodies as prothrombotic culprits in patients with COVID-19;¹⁹ these findings were not seen in our case. Indeed, our patient's coagulopathy workup did not reveal laboratory data to support a thrombotic etiology of his ischemic infarcts (Table 1). Notably, Yaghi and colleagues⁹ reported a 65.6% cryptogenic stroke rate in their data set of adult CoV-S; the remainder were ultimately classified as embolic of undetermined source. Their data suggest that the source of CoV-S may more often remain uncertain, even with clear and correlating clinical and radiographic findings, and require empirical management.

Although most reported cases of CoV-S have been unifocal or single territory, multifocal infarcts in different vascular territories have been described in at least two separate case series.^{24,25} The vascular imaging findings in our patient do not strictly adhere to a single subtype of childhood arteriopathy as categorized in the seminal Vascular effects of Infection in Pediatric Stroke study.⁶ Instead, the CoV-S experienced by our patient appears to have components of both a focal cerebral arteriopathy (i.e., proximal middle cerebral artery involvement and early isolated linear lentoculostriate infarct) and a vasculitis (i.e., multifocal infarcts with imaging-proven irregularities of multiple vessels). Despite comprehensive cardioembolic and coagulopathic workups (Table 1), neither revealed abnormalities sufficient to explain his strokes.

Seizures in children and adults who are COVID-19-positive have been recorded.¹⁸ The aforementioned Italian study reported seizures in five (3%) of their patients, with all but one of them having a history of seizure disorder.⁵ The seizure experienced by our patient is similarly confounded given his presentation with subacute hydrocephalus. Significant hydrocephalus itself may cause both seizure and large vessel steno-occlusion leading to infarction. However, the early placement of an EVD with normalization of intracranial pressure and reduction of ventriculomegaly, documented with interim negative MRI, and characteristic signs of arteriopathy on vascular imaging forced consideration of an alternative etiology.

SARS-CoV-2 nucleic acid was not detected by PCR in our patient's CSF (Table 1), which is not atypical according to currently available data. Several published studies have failed to detect SARS-CoV-2 in CSF samples, even in patients with COVID-19 who have overt neurological symptoms.¹⁹ A notable exception is the case reported by Mirzaee and colleagues.⁴ Elevated serum titers of cytokines, on the other hand, have been proposed as a source of the thrombophilia and immune-mediated encephalopathy seen in severe cases of COVID-19.²⁰ This should be distinguished from viral encephalitis, which by definition requires pleocytosis and elevated protein in CSF, concordant with direct invasion of and damage to neuronal and glial tissue by virus

particles. An encephalitic etiology was effectively ruled out in our patient based on uncharacteristic imaging and multiple normal CSF chemistries.

Although animal studies have suggested that SARS-CoV-2 neuroinvasion and dissemination can occur with sparse inflammatory markers, our patient's CSF demonstrated significantly elevated levels of IL-6 and IL-8 and, to a lesser degree, IL-2, IL-4, IL-10, and granulocyte-macrophage colony-stimulating factor (Table 1).¹⁹ Isolated elevation of CSF cytokines in absence of CSF pleocytosis is comparatively less reported, and its clinical significance is therefore less clear. However, these laboratory findings are most consistent with an endothelialitis. Infection and disruption of the cerebrovascular endothelium have been previously identified both radiographically and histologically in patients with COVID-19, some of whom were discovered to have concomitant cerebral thrombi and infarcts on autopsy.¹⁹ These findings, in combination with the SARS-CoV-2 IgG antibodies detected in his serum, suggest that our patient mounted a robust systemic immune response to his COVID-19 infection. However, this child did not meet US Centers for Disease Control and Prevention criteria for the multisystem inflammatory syndrome in children associated with COVID-19 because he lacked fever at presentation and had inflammation of only one organ system.²⁶

Lessons

These findings taken all together lead us to conclude that our patient developed an arteriopathy and had multiterritory strokes due to a primary or secondary immune response to circulating SARS-CoV-2. Although our patient presented with an asymptomatic infection, retrospective data sets have identified subgroups of COVID-19 infections that present only with neurological symptoms.^{10,18,19} We believe our case to be among a growing field of evidence describing the occurrence of multifocal stroke(s) secondary to COVID-19-induced arteriopathy in children.^{4,14-17} This case underscores the need for further investigation into the complex direct and indirect neurological sequelae of circulating SARS-CoV-2 antibodies in patients of all ages.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Magge, Foster. Acquisition of data: Magge, Foster. Analysis and interpretation of data: Magge, Foster, Wells. Drafting the article: Magge, Foster. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Magge. Administrative/technical/material support: Vargas, Keating. Study supervision: Magge.

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