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CASE REPORT

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Infantile ischemic stroke secondary to profound arteriopathy

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Abstract

Pediatric arterial ischemic stroke (AIS) is an uncommon emergency department (ED) presentation. We share the case of a 4-month-old female with a chief complaint of irritability and difficulty feeding. During ED evaluation, she developed lateral gaze deviation, tongue deviation, and rhythmic leg movements. Computed tomography of the head revealed a right-sided hypodensity concerning for ischemic infarct without hemorrhagic conversion. Subsequent brain magnetic resonance imaging and arteriography confirmed a large right-sided cerebral infarct and demonstrated narrowing and tortuosity of almost all extra- and intracranial vessels. Comprehensive pediatric AIS workup, including echocardiogram and laboratory tests for anemia, hypercoagulability, inflammatory, and genetic panels, were non-diagnostic. This case highlights the difficulty in diagnosis of pediatric AIS due to low clinical suspicion, limited neurologic examination, and non-specific presentations that may suggest stroke mimics. Maintenance of clinical suspicion and early recognition of pediatric AIS can result in earlier initiation of neuroprotective measures and optimization of imaging strategies for better outcomes.

KEYWORDS
arteriopathy, brain ischemia, imaging, infant, ischemic stroke, neurologic emergencies, pediatric, presentation, risk factors

1 | INTRODUCTION

Pediatric arterial ischemic stroke (AIS) is an uncommon but important cause of neurologic morbidity in children. Perinatal AIS, denoting stroke before 1 month of age, is estimated to affect 13–17/100,000 births, making the perinatal period one of the riskiest for stroke. The incidence of AIS declines considerably after 1 year.[1] Childhood AIS is estimated to occur in 2–3/100,000 children, most commonly because of arteriopathies, such as postinfectious focal cerebral arteriopathy, dissection, Moyamoya disease, or vasculitis.[1,2] Diagnosis of pediatric AIS is often delayed because of low clinical suspicion, limited neurological exam, non-specific presentations, and prevalence of stroke mimics (migraine, seizure, tumors, functional disorders).

We share a 4-month-old female presenting initially with irritability and poor feeding ultimately found to have right internal carotid artery (ICA) stroke secondary to profound arteriopathy of unknown etiology.

2 | CASE REPORT

A 4-month-old previously healthy, developmentally typical female was brought to the pediatric emergency department (ED) at a tertiary care hospital for one night of irritability and poor feeding. While in triage, her mother noticed intermittent rightward eye deviation. During initial ED assessment, she had normal vital signs (VS) for age. Physical

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examination showed midline gaze and non-focal neurologic examination with latching and breastfeed without difficulty. History was notable for up-to-date vaccinations and no recent sick contacts.

Given intermittent fussiness, the initial differential diagnosis included intussusception, dehydration, and gastroesophageal reflux. Abdominal ultrasound for intussusception was negative. On repeat assessment, she was noted to have persistent rightward eye deviation, leftward tongue deviation, and rhythmic jerking of the left leg, concerning for seizure activity. She was given intravenous lorazepam 0.1 mg/kg with resolution of jerking movements within minutes of administration but had persistent gaze and tongue deviation. With focal neurologic findings, the differential was broadened to include hemorrhage from non-accidental trauma or intracranial mass. Non-contrast computed tomography (CT) of the head revealed a large, right-sided hypodensity with loss of gray-white matter differentiation concerning for ischemic infarct. The patient was placed on stroke precautions, including frequent VS and neurologic assessments, and intravenous fluid hydration. Due to her young age, she was not a candidate for acute thrombolysis or thrombectomy. Magnetic resonance imaging and arteriogram (MRI/MRA) brain and neck were initially attempted in the ED with light sedation but ultimately required deep sedation by pediatric anesthesiology and was obtained en route to the pediatric ICU (PICU). The MRI/MRA revealed marked narrowing and tortuosity of the extracranial and intracranial vessels, most notably in the right ICA, right middle cerebral artery, and left proximal cerebral artery (Figure 1). A right-sided aortic arch with an aberrant left subclavian artery was noted.

In the PICU, she again had seizures that were treated with intravenous phenobarbital 20 mg/kg and intravenous levetiracetam 60 mg/kg. She was started on maintenance dosing of both medications for seizure prophylaxis and aspirin for secondary stroke prevention. She was monitored by video EEG for 24 hours, which did not show any additional seizure activity. Subsequent physical examination demonstrated left hemiparesis and rightward gaze preference.

Labs were notable for blood glucose level of 99 mg/dL, hemoglobin 10.6 g/dL, and elevated platelet count of 846 K/μL; hematology consultation attributed the latter 2 findings to normocytic anemia and reactive thrombocytosis, respectively. A comprehensive metabolic panel, hypercoagulability labs, and inflammatory markers were within normal limits. An echocardiogram to assess for evidence of structural abnormalities or thrombus was unrevealing. Cerebrospinal fluid studies were normal. The patient's complete medical evaluation is summarized in Table 1.

Repeat MRI/MRA brain on day 3 of hospitalization showed new right basal ganglia and white matter infarcts. Given her stenotic and tortuous vasculature, medical management prioritized maintenance of adequate cerebral perfusion with fluids and avoidance of hypotension.

The patient remained clinically stable and seizure-free. She was discharged home on hospital day 11 on daily phenobarbital 5 mg/kg, levetiracetam 40 mg/kg, and aspirin 5 mg/kg therapy, with plans for close follow-up and consideration of neurosurgical intervention after recovery from acute stroke. Results of genetic workup were pending. Discharge exam demonstrated improved antigravity movement of the left arm and leg, though less than the right, and her gaze preference had largely resolved.

2.1 | Follow-up and outcome

Hours after discharge, the patient returned to the ED with poor feeding, increased fussiness, and decreased right arm movement. Physical exam was notable for decreased strength and movement of the right arm, concerning for additional acute infarcts in the setting of relative dehydration. She was placed again on stroke precautions. An urgent, repeat MRI/MRA brain and neck revealed hyperacute bilateral infarcts in a watershed distribution. Laboratory workup was unremarkable. She underwent bilateral indirect extracranial-intracranial bypasses, a neurosurgical procedure typically used to treat Moyamoya vasculopathy by augmenting cerebral blood flow. Over the next 2 months, her exam demonstrated gradual, substantial improvement with symmetric vigorous movements, but with persistent subtle gaze preference and ongoing feeding difficulties requiring placement of gastrostomy tube.

The etiology of the patient's vasculopathy remains undetermined. Genetic panels for aortopathy, hereditary Moyamoya disease, and abnormalities in select cell regulatory pathways were negative. Ceruloplasmin and copper levels testing for Menkes' disease were normal. The patient was found to be heterozygous for a pathogenic variant in the adenosine deaminase 2 (ADA2) gene with an enzyme activity corresponding to a carrier level. Homozygous pathogenic variants can cause deficiency of the ADA2 enzyme associated with early onset small or medium-vessel stroke and vasculopathy, but it is not yet known if patients with carrier status can be symptomatic, and if so, to what degree. She is followed by neurology, genetics, and rheumatology as an outpatient.

3 | DISCUSSION

Physicians and other healthcare practitioners may have low clinical suspicion for pediatric AIS because of its relatively low incidence and atypical presentation when compared to other pediatric neurologic emergencies. There are approximately 5000 new diagnoses of pediatric AIS in the United States each year.[1] By contrast, there are about 795,000 adults with new or recurrent strokes each year.[3] Pediatric AIS is most often associated with arteriopathy (53%), cardiac disorders (31%), and infections (24%).[2] The most common arteriopathies are Moyamoya disease, focal cerebral arteriopathy, dissection, and vasculitis.[1,2] Recurrent pediatric AIS, especially in cases of underlying arteriopathy, is high, up to 66% within 5 years in 1 study.[4] Other risk factors for pediatric AIS include anemia, hypercoagulable states, dehydration, and recent viral infections.[5] Our patient had several of these factors initially and had relative dehydration at second presentation, which may have compounded risk for AIS. Conversely, strokes in older adults are commonly attributed to cardiac arrhythmias and atherosclerosis, which are atypical risk factors for pediatric AIS.[6]

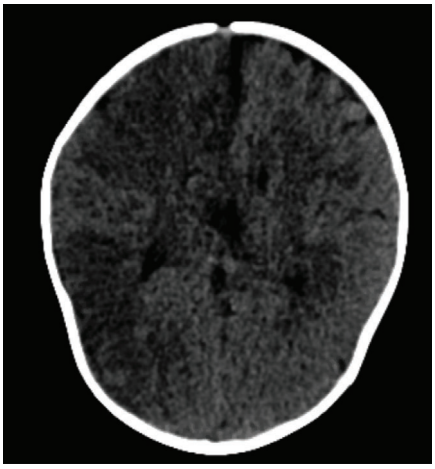
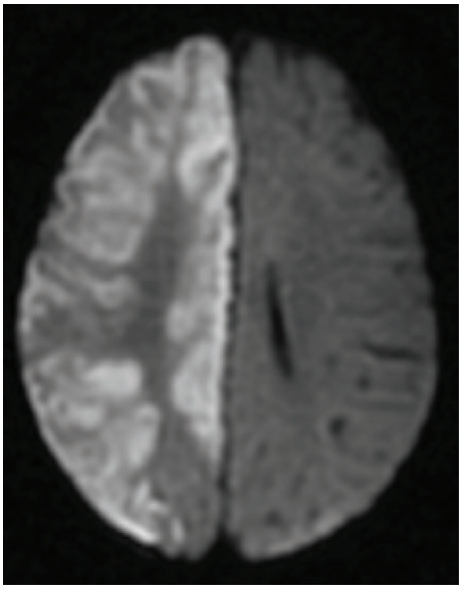
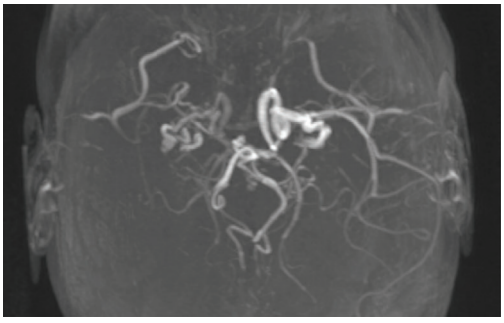
Imaging Modality	Image	Significant Findings
CT, non-contrast		Large hypodensities in the right cerebral hemisphere with loss of gray-white matter differentiation.
MRI, DWI		Widespread diffusion restriction (with ADC correlate, not shown here) in the distribution of the right anterior, middle, and posterior cerebral arteries.
MRA, bilateral intracranial and carotid vessels		Significant stenosis and tortuosity of the neck and intracranial vessels, most severe in the right internal carotid artery, bilateral middle cerebral arteries, distal basilar artery, and right posterior cerebral artery. Extensive collateral vessel formation, as in Moyamoya disease, was not visualized.

FIGURE 1 Radiologic findings and representative cross-sectional imaging of brain and neck. Abbreviations: ADC, apparent diffusion coefficient; CT, computed tomography; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging

TABLE 1 Etiology-based summary of patient's evaluation

Etiology	Evaluation studies	Results
Cardioembolic	Echocardiogram, transthoracic and transesophageal	Normal bilateral ventricular size and function
		No thrombus or shunt
		Right aortic arch with aberrant right subclavian artery
		No valvular disease or aortic root dilation
Hematologic/thrombotic	CBC	Normocytic anemia
		Thrombocytosis
	PT, PTT, INR	Normal
	Hypercoagulability studies	Negative for hemoglobinopathy, antiphospholipid antibody syndrome, inherited coagulation regulatory protein deficiency, factor V Leiden or prothrombin mutation
		Homocysteine level within normal limits
Genetic/Inherited	Physical exam	No dysmorphic or cutaneous stigmata to suggest PHACES, Williams syndrome, trisomy 21, neurofibromatosis, or Alagille syndrome
	Genetic panels	Negative for Noonan spectrum disorder, aortopathy, Moyamoya disease, and RASopathy
	Menkes disease workup	Serum copper and ceruloplasmin levels within normal limits
	Deficiency of ADA2 workup	Heterozygous for pathogenic variant of ADA2 gene
		Plasma ADA2 catalytic activity consistent with carrier status
Infectious	Viral respiratory panel	Negative
	SARS-CoV-2 PCR	Negative
	CSF	Normal
Inflammatory	CRP, ESR, D-dimer	Normal

Abbreviations: ADA2, adenosine deaminase 2; CBC, complete blood count; CSF, cerebral spinal fluid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; PCR, polymerase chain reaction; PHACES, posterior fossa brain malformations, hemangioma, arterial lesions, cardiac abnormalities, and eye abnormalities syndrome; PT, prothrombin time; PTT, partial prothrombin time; RASopathy, disorder within the rat sarcoma virus pathway.

Evaluation of pediatric patients is challenging due to developmental abilities, variable cooperation with exam, and non-specific exam findings. The neurologic exam may be especially difficult in children who are developmentally delayed or have neurological comorbidities. Infants with AIS may present subtly with irritability and decreased movement.[6,7] Children and young adults, however, may present similarly to adults with headache, seizures, unilateral weakness, aphasia, visual field cuts, or cerebellar signs.[8] Notably, headache and seizures are far more typical of pediatric stroke presentations, found in as many as 50% and 37% of children aged 29 days to 18 years, respectively.[9]

As soon as AIS is suspected, physicians and other healthcare practitioners should institute neuroprotective measures, which include stabilization of airway, breathing, and circulation; targeted blood pressure management; and aggressive seizure control. Administering antiepileptics prophylactically is not generally recommended.[6] Specific recommendations for management and neuroimaging should be discussed with a pediatric neurologist. Appropriate next steps should include assessment of the patient's age and developmental stage to expedite imaging: ability to tolerate brain imaging, sedation needs, CT and MRI scanner availability, and need for nursing, respiratory, and/or ancillary staff at bedside. A non-contrast CT head can be obtained emergently for patients with suspected hemorrhage or contraindications to MRI but is less sensitive for evaluating acute ischemia than MRI with diffusion-weighted imaging.[10,11] CT is unable to distinguish between common pediatric stroke mimics, such as posterior reversible encephalopathy syndrome or methotrexate leukoencephalopathy. Ionizing radiation from CT is another important consideration: children are highly radiosensitive and may have a 2- to 3-fold greater lifetime cancer risk than a population exposed at older ages.[12] Finally, MRA provides valuable information regarding vessel patency, caliber, tortuosity, and distribution that are essential in stroke evaluation.

Tissue-type plasminogen activator is not approved by the Food and Drug Administration for pediatric AIS but has been used off label for hyperacute intravenous thrombolysis.[13] Its use may be discussed with a neurologist for pediatric thrombotic stroke patients within 4.5 hours of symptom onset.[11] Candidacy for endovascular therapy may be an option for some children with acute large vessel occlusion. There is a paucity of data for long-term outcomes in pediatric stroke survivors, though are they are felt to be better than those in adult survivors given an overall decline in neuroplasticity with age.[14]

This case highlights the difficulty of diagnosing pediatric AIS because of low prevalence, non-specific clinical presentations, and frequency of stroke mimics. A high index of suspicion is paramount in the evaluation of a pediatric patient with possible ischemic stroke, as early

diagnosis facilitates neuroprotection and optimal imaging modalities for improved outcomes.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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