Stroke

SPECIAL REPORT

Mechanical Thrombectomy for Acute Ischemic Stroke

Considerations in Children

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ABSTRACT: The use of mechanical thrombectomy for the treatment of acute childhood arterial ischemic stroke with large vessel occlusion is increasing, with mounting evidence for its feasibility and safety. Despite this emerging evidence, clear guidelines for patient selection, thrombectomy technique, and postprocedure care do not exist for the pediatric population. Due to unique features of stroke in children, neurologists and interventionalists must consider differences in patient size, anatomy, collateral vessels, imaging parameters, and expected outcomes that may impact appropriate patient selection and timing criteria. In addition, different causes of stroke and comorbidities in children must be considered and may alter the safety and efficacy of thrombectomy. To optimize the success of endovascular intervention in children, a multidisciplinary team should take into account these nuanced considerations when determining patient eligibility, developing a procedural approach, and formulating a postprocedure neurological monitoring and therapeutic plan.

Key Words: acute stroke ■ internal carotid artery ■ magnetic resonance angiography ■ middle cerebral artery ■ patient selection ■ thrombectomy

As treatment options for acute stroke in adults drastically expand, care of childhood stroke remains largely based on extrapolation from adult data. Case series and retrospective analyses suggest that mechanical thrombectomy (MT) may be feasible and safe in some pediatric patients with stroke.[1–7] However, clear guidelines for patient selection, thrombectomy technique/devices, and postprocedure care do not exist for the pediatric population. Study of this population is greatly needed due to unique features of pediatric stroke that may impact safety and efficacy of MT. Through a case-based approach, we review critical considerations for MT that are specific to children.

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The children undergoing thrombectomy presented here were diagnosed at Children's National Hospital, where magnetic resonance imaging (MRI) is available during daytime hours and decisions regarding IV tPA (intravenous tissue-type plasminogen activator) are made using CT and CT angiography (CTA) overnight. Thrombectomy candidates are emergently transferred to the Johns Hopkins Children's Center, a thrombectomy-capable children's center within a comprehensive stroke center. Protocol for suspected strokes at Johns Hopkins is emergent brain MRI, including diffusion-weighted, susceptibility-weighted, and arterial spin labeling perfusion sequences, as well as time-of-flight magnetic resonance angiogram of the head. If intracranial hemorrhage is suspected, or if MRI is contraindicated, CT/CTA is obtained instead. CT perfusion is added when intervention is being considered after 6 hours from the last time the child was seen well.

CASE-BASED CONSIDERATIONS

Case 1

A 4-year-old girl with congenital heart block and a dual-chamber pacemaker presented with acute-onset

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Nonstandard Abbreviations and Acronyms

CTA	CT angiography
ECMO	extracorporeal membrane oxygenation
IV tPA	intravenous tissue-type plasminogen activator
MT	mechanical thrombectomy
TIPS	Thrombolysis in Pediatric Stroke
WARCEF	Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction

left-sided weakness and right gaze deviation. Pediatric National Institutes of Health Stroke Scale score was 11. Head CT 2 hours after symptom onset was normal with Alberta Stroke Program Early CT Score (ASPECTS) of 10. CTA demonstrated occlusion of the right middle cerebral artery at its origin. She was treated with 0.9 mg/kg IV tPA 3 hours after symptom onset with 10% given as a bolus and the remaining 90% infused during transport by air to the nearest pediatric thrombectomy-capable center. Groin puncture was at 4 hours after symptom onset, and Thrombolysis In Cerebral Infarction grade 3 recanalization (5 passes, stent retriever and aspiration) was achieved 6 hours after symptom onset. After the procedure, the child's weakness improved and gaze deviation resolved. However, 18 hours postintervention, the child's hemiparesis worsened. Emergent head CT/CTA revealed an infarct confined to the right basal ganglia and patent cerebral arteries. Transthoracic echocardiogram revealed profound heart failure. Hemiparesis improved with treatment of her heart failure, suggesting the worsening deficit was secondary to poor cerebral perfusion. At follow-up 9 months poststroke, Pediatric Stroke Outcome Measure was 1 for a moderate motor deficit.

Considerations

Should I Consider IV tPA in Children Who Are Thrombectomy Candidates?

To date, no randomized controlled trial has compared the efficacy of MT alone to IV tPA plus MT for the treatment of acute arterial ischemic stroke. In the landmark trials that demonstrated improved outcomes with thrombectomy as compared with IV tPA alone for large vessel occlusion, most patients treated with MT were also treated with IV-tPA.[8] It is possible that preceding treatment with IV tPA modifies the clot, making it easier to extract. However, IV-tPA also increases hemorrhage risk[9,10] and could theoretically contribute to delays in the time from emergency department arrival to groin puncture. A meta-analysis of 12 retrospective studies of 2615 adults treated with either MT alone or IV tPA plus MT showed no difference between the 2 groups in time to recanalization, Thrombolysis In Cerebral Infarction grade, symptomatic intracranial hemorrhage, or all-cause mortality at 90 days.[11] There was, however, a trend toward a greater proportion of patients with modified Rankin Scale score 0 to 2 at 90 days in the IV tPA plus MT group. Similarly, no significant differences between patients treated with MT alone and IV tPA plus MT were reported in smaller-scale analyses of registry data and post hoc trial data.[8,12,13] As such, it remains to be determined by an adequately powered randomized trial whether preceding treatment with IV tPA impacts outcomes after MT.

Data are even more sparse in children owing to absence of randomized controlled data to support the efficacy of IV tPA. The TIPS trial (Thrombolysis in Pediatric Stroke), a safety and dose-finding study of IV tPA in children, was closed early due to lack of participant accrual.[14] Though recent retrospective data suggest that the risk of symptomatic intracranial hemorrhage in children who receive IV tPA within 4.5 hours of stroke onset is low, about 2.1%,[15] the efficacy of IV tPA in children remains unknown. In addition, the optimal IV tPA dosing in children is also unknown and likely differs from the adult weight-based dosing due to developmental hemostatic changes, including lower levels of plasminogen and endogenous tPA in young children,[16] such as the child in this case. Despite the lack of data on efficacy and appropriate dosing, IV tPA is administered to about 2% of children with stroke,[17,18] and we consider administration in children who meet criteria per the Thrombolysis in Pediatric Stroke trial.

Are There Any Specific Considerations for Children With Congenital Heart Disease?

Congenital heart disease is a major risk factor for childhood stroke,[19,20] and the level of suspicion for stroke must be high in this population, especially because stroke diagnosis may be delayed due to sedation and neuromuscular blockade.[21] A pacemaker may preclude the use of MRI, adding an additional diagnostic challenge in these children.

Each child's specific cardiac anatomy and function must be carefully considered to understand stroke pathogenesis, navigate complex anatomy during MT, and optimize cerebral perfusion during and after the procedure. In this case, the child had a structurally normal heart. Lack of atrial-ventricular synchrony related to pacemaker malfunction leading to intracardiac thrombus was considered, but the pacemaker was functioning appropriately. Instead, heart failure was felt to be the cause of her stroke.

Cerebral oxygen delivery is determined both by arterial oxygen content and cardiac output. In infants and children with complex congenital heart disease, cardiac output maldistribution frequently occurs resulting in congestive heart failure, pulmonary edema, hypoxemia (either due to intracardiac or intrapulmonary shunting), and low systemic blood flow with resultant decreases

in cerebral oxygen delivery. Optimizing cerebral oxygen delivery sometimes entails losing the neurological examination. For example, in patients with pulmonary hypertension, neuromuscular blockade, sedation, and mechanical ventilation may be required to ensure adequate systemic cardiac output and oxygenation. In the case presented here, meticulous fluid management, contractility agents, and vasoactive medications were needed to maintain the child's cerebral perfusion.

What Is the Optimal Timing of Starting Anticoagulation After MT for a Cardioembolic Stroke, if Indicated?

The risk of stroke recurrence in children with congenital heart disease is ≈27% at 10 years and is highest within the first 6 months after a first stroke.[22] Several factors should be considered before initiating antithrombotic therapy including infarct size, use of recanalization treatments, urgency of anticoagulation, and fontanelle patency (a pop-off in case of hemorrhage that may decrease herniation risk or associated mortality). The timing of anticoagulation initiation after stroke is based on the assessment that recurrent stroke is a greater clinical concern than the bleeding risk at a specific point in time.

Following cardiac surgery using cardiopulmonary bypass for congenital heart disease, the incidence of perioperative stroke may be as high as 10%.[21,23] MT may be the only acute stroke therapy for which the child is eligible in the postoperative setting. After MT, benefits of anticoagulation need to be balanced against the potential for postoperative bleeding with fresh suture lines.

As in adults, it is reasonable to obtain neuroimaging 24 hours after MT to assess for intracranial hemorrhage. In the absence of hemorrhagic conversion, it may be reasonable to initiate antithrombotic therapy as early as 24 hours after MT,[24] though data supporting this timeline in children are lacking. If hemorrhagic transformation is present, delay in antithrombotic therapy initiation should be considered. In a single-center study of 63 children with stroke, 56% of children with supratentorial infarct volume ≥5% of the supratentorial brain volume experienced hemorrhagic transformation within 30 days after stroke, though most bleeds were petechial and asymptomatic.[25] With small, asymptomatic hemorrhage, the risks and benefits of antithrombotic therapy should be weighed. Though data on recurrence risk after a cardioembolic stroke are minimal, certain conditions (eg, mechanical heart valves, intracardiac thrombus, and intracardiac right-to-left shunting) have high risk of stroke, and anticoagulation should be started as soon as the bleeding risk has decreased.[26,27] With regards to patients with low ejection fraction, one study suggested that children with dilated cardiomyopathy and fractional shortening <20% should be treated with anticoagulation to prevent thromboembolic events,[28] though this is not a universal standard practice. Based on the WARCEF trial (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) in adults,[29] it may be advisable to start anticoagulation in children when the ejection fraction is <30%. Currently, there is no consensus on when to start anticoagulation and most evidence in children is based on retrospective studies rather than randomized controlled trials.

What Should Be Done for Post-Thrombectomy Worsening of Neurological Status?

Worsening of neurological status after thrombectomy should raise concern for intracranial hemorrhage, reocclusion of the affected artery, vasospasm, or recurrent stroke in a different vascular territory. Emergent neurovascular imaging should be considered for any change in neurological examination. In this case, worsening deficits were due to global hypoperfusion and were reversed with correction of the heart failure.

Can I Consider Thrombectomy in Children on ECMO?

Though the child in this case did not require extracorporeal membrane oxygenation (ECMO), pediatric MT has been performed at our institution while a child was on ECMO.[30] Stroke (hemorrhagic or ischemic) occurs in 12% of children on ECMO.[31] Stroke recognition is difficult in these patients due to intubation and prevalent use of paralytics and sedatives, but asymmetries may be detected on routine neurological examination, surveillance head ultrasound, and electroencephalogram. As these children are not candidates for IV tPA due to bleeding risk at the cannulation site and ongoing heparin administration, MT is the only hyperacute therapy for which children on ECMO may be eligible. Transporting the ECMO circuit to the neurovascular suite is feasible but can be a herculean task, requiring coordination between intensivists, neurologists, interventionalists, radiology technologists, perfusionists, nurses, and respiratory therapists. Technical complexity also depends on cannulation site. Carotid catheterization in venoarterial ECMO limits access to the cerebral circulation. For right anterior circulation clots, the risk of crossing from the left carotid to a right-sided occlusion during MT would potentially jeopardize the left internal carotid artery, middle cerebral artery, and anterior cerebral artery territories, with risk, therefore, likely outweighing any potential benefit, particularly if the right carotid is anticipated to be sacrificed. In addition to these technical challenges, risks in these children are high due to significant underlying illness. Furthermore, the ongoing need for anticoagulation during ECMO may increase bleeding risks, both at the puncture site and intracranially from hemorrhagic conversion of ischemic tissue. Given the high risks of MT in children on ECMO, risks and benefits must be carefully weighed.

Case 2

An 11-year-old boy was unresponsive upon presentation after a gunshot wound to the chest. Head CT was normal. After laparoscopic repair of the left diaphragm, he became

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asystolic and received 17 minutes of cardiopulmonary resuscitation. After return of spontaneous circulation, a bedside thoracotomy resulted in identification and repair of a left ventricle laceration. Neurology was consulted several hours later per standard postarrest care. The exam revealed an intubated patient who awakened to moderate stimulation and could follow 1-step commands. Cranial nerve exam revealed a left internuclear ophthalmoplegia. Brain MRI (≈24 hours postgunshot and 18 hours postarrest) showed multiple, small ischemic infarctions in the cerebellum, midbrain, and pons from a basilar artery thrombosis (Figure 1). CTA confirmed absent flow in the distal basilar and bilateral superior cerebellar arteries. A successful basilar artery thrombectomy (Thrombolysis In Cerebral Infarction grade 3, single pass with a stent retriever) was performed 40 hours after the gunshot wound (Figure 1). Follow-up MRI/magnetic resonance angiography 1-month later demonstrated no interval infarction and normal cerebral vasculature. Six months postinjury, the child had a partial left visual field cut but was back in school and performing at baseline without motor deficits.

Considerations

What Is the Role of Neurological Assessments in Intubated and Sedated Patients?

Critical illness is an important risk factor for pediatric stroke, and stroke must be considered when there is a new focal deficit in any child requiring intensive care. In this case, the internuclear ophthalmoplegia in a child with cardiac dysfunction, a risk factor for cardioembolic stroke, prompted concern for stroke. Routine neurological assessments in intubated and sedated children can be critical in early stroke identification and treatment.

What Should Be Considered When There Is a Delay to Thrombectomy?

The therapeutic window for MT in children may extend beyond the established window for the adult population, but there are no high-quality data that establish timing parameters for pediatric thrombectomy. Increasingly recognized in the adult population is the importance of collateral perfusion and other patient-specific factors in determining appropriate time windows for intervention. This has led to more imaging-based, as opposed to time-based, patient selection for thrombectomy.[32] Perfusion imaging plays a pivotal role in selecting candidates for MT in adults who present with acute stroke between 6 and 24 hours from the time they were last seen well.[33,34] Perfusion imaging is also feasible in children presenting with acute stroke symptoms, but optimal penumbral thresholds may differ from adults.[35] Further studies defining neuroimaging parameters that identify pediatric patients with stroke likely to benefit from thrombectomy are needed.

Though data are sparser in children, there are numerous reports of successful thrombectomy in children in an extended time window, even with a delay of 2 to 3 days.[36–38] Most cases of successful delayed recanalization involve the posterior circulation, perhaps related to clinicians' willingness to extend the traditional time window when the outcome is expected to be poor, such as in basilar artery occlusions. Our patient not only suffered hemorrhagic shock leading to cardiac arrest, but his posterior circulation tolerated a basilar artery occlusion for a prolonged period of time with only small infarctions and little clinical impact. One may hypothesize a more extensive collateral supply in children that allows for successful intervention in a longer time window. While animal studies suggest that immature rodents are able to recruit a more extensive network of collateral vessels in the setting of stroke compared with their adult counterparts,[39] this has not been adequately studied in infants and children. Further study is needed to determine the therapeutic window for MT in children.

Case 3

A 9-month-old previously healthy girl with a mild upper respiratory infection presented with right hand and face

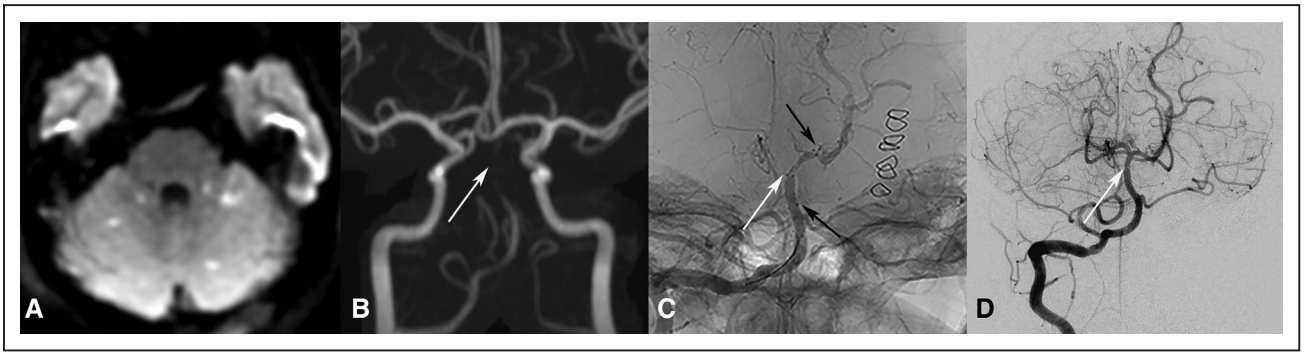

Figure 1. A 13-year-old with basilar artery occlusion after cardiac arrest secondary to gunshot wound.
Axial diffusion-weighted image (**A**) demonstrates multifocal areas of restricted diffusion in the bilateral cerebellar hemispheres with overall preservation of the brain stem. Magnetic resonance angiography maximum intensity projection image (**B**) shows occlusion of the mid basilar artery (white arrow). Right vertebral artery unsubtracted anteroposterior view (**C**) shows the stent retriever (black arrows) across the site of the basilar occlusion (white arrow) and into the left P1 segment, resulting in Thrombolysis In Cerebral Infarction grade 3 recanalization (**D**). Mild spasm (arrow, **D**) is present at the level of the previous occlusion.

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twitching followed by dense hemiparesis. MRI demonstrated a large area of left middle cerebral artery territory restricted diffusion without fluid attenuation inversion recovery change. MT was considered but not pursued due to large infarct core and tapering appearance of the left internal carotid artery terminus, concerning for an arteriopathy (Figure 2). Over the course of weeks, the arteriopathy progressed bilaterally, and she was diagnosed with moyamoya disease. She suffered multiple additional strokes. She ultimately underwent bilateral indirect revascularization procedures with clinical stability and cessation of ongoing strokes 4 months postprocedure.

Considerations

What Imaging Appearances Suggest High Risk of Thrombectomy?

Though this child met adult criteria for MT, extra caution was warranted because the mechanisms of pediatric stroke differ from adult stroke. Arteriopathies, including focal cerebral arteriopathy, moyamoya vasculopathy, and dissection, are present in over half of childhood stroke cases.[40] Endovascular therapies are likely higher risk when arteriopathy is present, with concerns of additional vascular injury, inflammatory response exacerbating stenosis, increased risk of dissection in an inflamed vessel, expansion of intimal tear in a dissected vessel, and increased risk of vasospasm and vessel rupture.[41,42] In one study of adults with cervical artery dissection, there was a nonsignificant increase in the incidence of symptomatic intracranial hemorrhage and 90-day mortality in patients who received thrombectomy compared with those who did not.[43] Despite concerns about vessel fragility, in the Save ChildS study, a multicenter study of 73 children who underwent thrombectomy, there were no dissections or vessel ruptures, including in 14 children with arteriopathies.[1] The authors hypothesize a potential selection bias against children with suspected inflammatory arteriopathies, though they also astutely note that the stroke cause is often unknown at the time of the decision to pursue MT.

In addition to safety concerns, thrombectomy is also less likely to be effective in arteriopathic stroke, as ischemia is often related to cerebral territorial hypoperfusion rather than a discrete embolism. Unlike embolic strokes, thrombectomy does not resolve the underlying cause of decreased perfusion in arteriopathic strokes, and therefore, early stroke recurrence may be common due to thrombus reformation at the site of aberrant blood flow.

Therefore, with an imaging appearance concerning for arteriopathy, such as a tapering vessel as opposed to an abrupt cutoff, the risks of thrombectomy should be considered. Acknowledging these important points, thrombus formation proximal to the stenotic portion of the vessel due to decreased flow may be amenable to MT in carefully selected cases. In the setting of an acute occlusion, if the benefits of intervention are felt to outweigh risks, one might consider aspiration techniques instead of stent retrieval techniques to minimize vascular endothelial damage.[44–46] However, despite in vitro studies supporting the idea that aspiration might be safer than stent retrievers in arteriopathies, a subanalysis of the Save ChildS study did not show any association between device and recanalization rate, complication rate, or neurological outcome.[47] As there were only 7 children in the aspiration group in Save ChildS and device selection was not randomized, introducing the possibilities of underpowering and selection bias, future investigation focused on selection of devices based on patient and mechanistic considerations is needed.

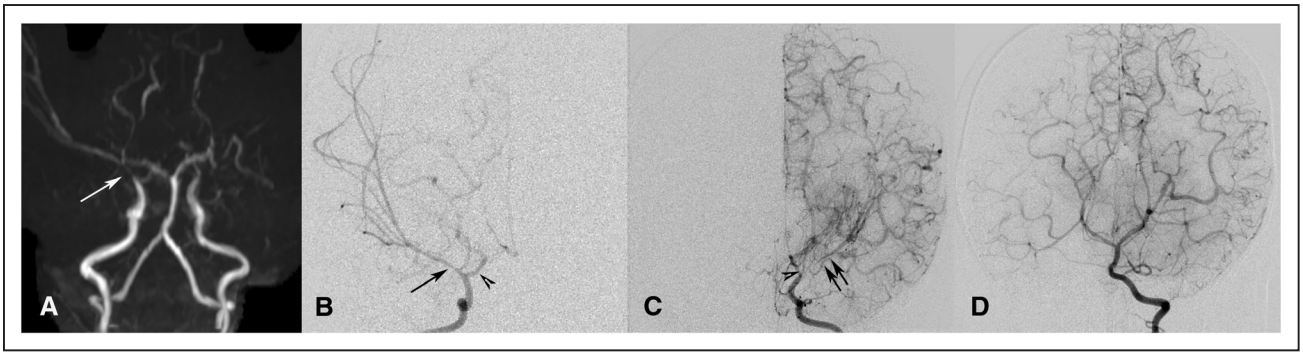

Figure 2. A 9-month-old girl with moyamoya disease.
Magnetic resonance angiography maximum intensity projection (**A**) shows high-grade tapering of the right internal carotid artery (ICA) terminus (arrow) extending into the right M1 and poor opacification of the right anterior cerebral artery (ACA). Left ICA high-grade stenosis is also present with poor filling of the left ACA and middle cerebral artery (MCA). The posterior circulation is unremarkable. Cerebral anteroposterior views from right ICA, left ICA, and left vertebral artery angiograms show characteristic features of moyamoya disease. Right ICA (**B**), the posterior communicating artery (open arrowhead) supplies the right posterior cerebral artery (PCA) territory. High-grade terminal ICA stenosis (arrow) extends into the M1 segment. The anterior choroidal artery is minimally hypertrophied and the right A1 segment is faintly seen. Left ICA (**C**), the posterior communicating artery (open arrowhead) supplies the left PCA territory. The left ICA is occluded distal to the anterior choroidal artery and hypertrophied lenticulostriate collaterals reconstitute the left MCA (double arrows). Left PCA to MCA pial collaterals are also seen. Left vertebral artery (**D**), robust collateral supply to the bilateral cerebral hemispheres is seen, left more than right, with characteristic PCA to MCA collaterals and perisplenial PCA collaterals backfilling the ACA territory.

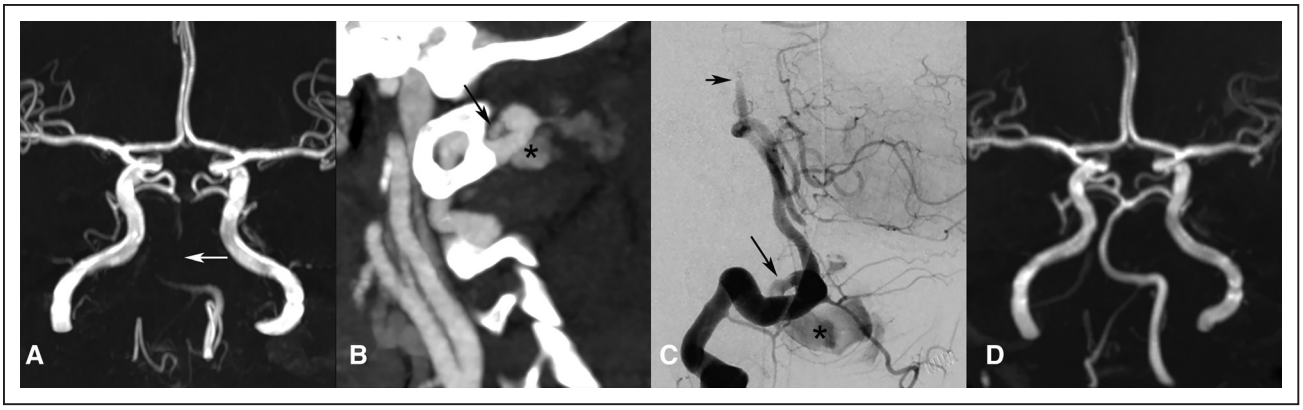

Figure 3. A 14-year-old with acute basilar artery occlusion and imaging concerning for possible connective tissue disorder. Magnetic resonance angiography (MRA) maximum intensity projection (MIP; **A**) shows occlusion of the mid to distal basilar artery (arrow). Sagittal CT angiography reconstruction (**B**) shows an enlarged left paravertebral vein (asterisk) and a feeding artery (arrow) arising from the left V3 segment. Lateral (**C**) view from a left vertebral artery angiogram shows the basilar occlusion (short arrow) and early opacification of the dilated left paravertebral vein. Follow-up MRA MIP (**D**) 6 wk later shows recanalization of the basilar artery, with minimal residual irregularity.

What Medical Comorbidities Increase the Risk of Endovascular Therapy?

In contrast to systemic thrombolysis, MT has relatively few medical contraindications. Exclusion criteria common to many of the adult thrombectomy trials include sustained hypertension, hypo- or hyperglycemia, thrombocytopenia, coagulopathy, severe electrolyte disturbances, recent cerebral infarction in the distribution of the relevant occluded artery, and terminal illness. Some risk factors for childhood stroke, such as connective tissue disorders, may also increase the risk of thrombectomy.[48] For example, patients with Ehlers Danlos type IV are at high risk for complications including death after angiography.[49,50] When diagnostic angiography is suggestive of connective tissue disorder, MT may be aborted given the significantly increased risk of arterial injury in the setting of underlying connective tissue disorder (Figure 3). The risks of general anesthesia may also be higher in children with some underlying medical conditions and in children with cerebral arteriopathies, in whom transient hypotension related to anesthesia induction may provoke stroke.

Given Better Outcomes of Childhood Stroke Compared With Adults, How Do We Decide Which Children Will Benefit From MT?

The good outcomes that have been reported in uncontrolled studies of MT for childhood stroke with large vessel occlusions must be interpreted in the context of a more favorable natural history of stroke compared with adults. Basilar artery occlusions, for example, are considered devastating in adults but do not portend the same dismal prognosis in children. Of children with basilar artery occlusion, there is a 92% survival rate and 46% rate of good outcome (modified Rankin Scale score, 0–2).[51] This contrasts with adult basilar artery occlusion, which has a reported survival rate of 64% and a favorable outcome rate of <25%.[52] Regardless, most children have persistent impairment after stroke, and deficits are often severe.[53] The potential for poor outcome, in conjunction with mounting evidence of the safety of MT in children, suggests that it is reasonable to consider MT if it can be done safely by an interventionalist with sufficient pediatric experience.

CONCLUSIONS

The use of MT for treatment of acute childhood arterial ischemic stroke is increasing, with mounting evidence of its safety and efficacy. Neurologists must consider differences in patient size, anatomy, collateral vessels, imaging parameters, and expected outcomes that may impact appropriate patient selection and timing criteria. In addition, different causes of stroke and comorbidities in children must be considered and may alter the safety and efficacy of thrombectomy. Endovascular intervention in children should take into account these nuanced considerations.

ARTICLE INFORMATION

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