Acute Ischemic Pediatric Stroke Management: An Extended Window for Mechanical Thrombectomy?

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Ischemic stroke is a rare condition to afflict the pediatric population. Congenital cardiomyopathy represents one of several possible etiologies in children. We report a 9-year-old boy who developed right middle cerebral artery stroke secondary to primary restrictive cardiomyopathy. In the absence of pediatric guidelines, the child met adult criteria for mechanical thrombectomy given the small core infarct and large penumbra. The literature suggests children may benefit from mechanical thrombectomy in carefully selected cases. Our patient exemplifies specific circumstances in which acute stroke therapy with thrombolysis and thrombectomy may be safe.

Keywords: cerebral infarction, stroke, child, restrictive cardiomyopathy, management, tissue plasminogen activator, mechanical thrombectomy

BACKGROUND

Pediatric arterial ischemic stroke is a rare condition with an estimated incidence of 1.6/100,000 children/year (1, 2). Its diagnosis is challenging because roughly 50% of the children afflicted bear no known vascular risk factor. Low-clinical suspicion rates coupled with a high variability of presentations often lead to a significant diagnostic deferral (3). Furthermore, despite a cohort of documented risk factors, one-third of stroke diagnoses are characterized as cryptogenic (4). In essence, the absence of established treatment guidelines burdens therapeutic decision-making and possibly children’s outcomes.

Adult populations benefit from systematic acute stroke management evidence (5–8). Conversely, current pediatric guidelines are based upon weak evidence and expert consensus owing to a heterogeneous pathophysiology, and inherent enrolling limitations (9). The efficacy and safety of intravenous thrombolysis use in children is not well defined (10–12). Further therapies such as intra-arterial thrombolysis and mechanical revascularization need additional investigation. Encouraging efforts provide a framework for future prospective trials (13–16). This manuscript contributes to

Abbreviations: CCM, congenital cardiomyopathy; CHD, congenital heart disease; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale; PRCM, primary restrictive cardiomyopathy; TICI, thrombolysis in cerebral infarction; TIPS, Thrombolysis in Pediatric Stroke; r-tPA, recombinant tissue plasminogen activator; IV, intravenous; RCPCH, Royal College of Pediatrics and Child Health.
the current literature on successful pediatric stroke management with thrombolysis and mechanical thrombectomy and advocates for a window of opportunity for improved outcomes. Oral and written informed consent was obtained from the parents of the child whose case is herein reported.

**INTRODUCTION**

A 9-year-old boy with no known past medical history presented with left hemiparesis, hemihypesthesia, and dysarthria. There had been no witnessed seizure activity. He was last noted to be at neurologic baseline 5.5 h earlier, before sleep. The initial community emergency room diagnosis was Todd’s paralysis. He received intravenous lorazepam and a loading dose of phosphonytine. When there was no clinical improvement 2 h later, an emergent neurological consultation recommended a computed tomography (CT) of the head. The CT head demonstrated an evolving right middle cerebral artery (MCA) stroke. The presence of a “hyperdense MCA sign” on CT suggested a proximal MCA occlusion. The patient was immediately transferred to our tertiary–quaternary care center.

On arrival, he was afebrile, with HR 120 bpm, BP 168/116, SO2 99% on room air. Physical examination was notable for mild jugular venous distension and a loud P2 sound on cardiac auscultation. There was no hepatomegaly or ascites. EKG showed biaxial enlargement. He followed two-step appendicular (right-sided) commands, with an overall Pediatric National Institute of Health Stroke Scale score of 7. Brain magnetic resonance imaging (MRI) and angiogram of head and neck was significant for a right insular region infarction, as well as a right (M1 segment) MCA occlusion. Perfusion-weighted imaging was also obtained, which demonstrated significantly increased mean transit time. The stroke volume was calculated to be 6 cc by the ABC/2 method (17). A large area of perfusion deficit, coupled with small area of infarction, is what is commonly referred to as a large perfusion/diffusion mismatch (Figure 1). The large area of perfusion/diffusion mismatch observed in this patient is a relative indication for pursuing treatment.

**Management**

Seven hours after last seen at baseline, our child was significantly outside of the intravenous recombinant tissue plasminogen activator (IV r-tPA) therapeutic window. The recommended pediatric IV r-tPA window is 3–4.5 h after last known normal (9). However, he was deemed a suitable candidate for endovascular recanalization given the small core infarct and large penumbra. The patient was taken to the neuroendovascular suite and intubated. A 5 French (Fr) sheath was placed in the right common femoral artery and a 5 Fr 90 cm Envoy (Codman & Shurtleff, Inc., Raynham, MA, USA) was navigated into the distal cervical right internal carotid artery (ICA). Right ICA injections showed a right M1 segment MCA occlusion just distal to the origin of the right anterior temporal artery (Figures 2A,B). Successful mechanical thrombectomy was performed with a 3 mm × 20 mm Trevo retrievable stent device (Stryker Neurovascular, Fremont, CA, USA). Two passes with the Trevo were performed while under continuous aspiration through the base catheter during retraction of the retrievable stent. Thrombolysis in cerebral infarction (TICI) 3 right MCA recanalization was achieved within 1.5 h of completion of the MRI, for a total time between symptom onset to recanalization of 8.5 h. This procedure was complicated by thromboembolic occlusion of the A2 segment of the right anterior cerebral artery (Figure 2).

An urgent transesophageal echocardiogram confirmed bilateral severe atrial enlargement with normal ventricular size and function, with cardiac MRI confirming the diagnosis of restrictive cardiomyopathy and the absence of an intracardiac thrombus (Figure 2). A right ventricular endomyocardial biopsy showed cardiomycocyte hypertrophy with endocardial and superficial interstitial fibrosis.

Subsequently, anticoagulation with dabigatran was prescribed for secondary stroke prevention. Given his high risk for arrhythmia, an implantable cardiac defibrillator was placed. His hypercoagulable work-up was negative. Genetic testing revealed a missense mutation in the TNNI3 gene consistent with a primary restrictive cardiomyopathy (PRCM). Following the diagnosis of PRCM, a detailed history revealed frequent episodes of lip cyanosis when swimming or biking, which caused him to avoid physical exertion. This behavior had become progressively obvious to his relatives, who had attributed his inactivity to “being lazy.” On discharge, his examination was only notable for a left pronator drift (NIHSS 1), with a modified Rankin score of 1. Four months later, he underwent a successful heart transplant and at 1-year follow up, he continued to be without thromboembolic sequelae and neurologically stable.

**DISCUSSION**

**Primary Restrictive Cardiomyopathy**

Primary restrictive cardiomyopathy accounts for 2.5–5% of cardiomyopathies in children. It is characterized by biaxial enlargement, normal left ventricular wall thickness and atrioventricular valves, impaired ventricular filling with restrictive physiology, and preserved systolic function (18–21). Most commonly PRCM is idiopathic in nature (20, 22). Other etiologies involve genetic disorders, skeletal myopathies, and storage diseases (23, 24).

Atrioventricle is the most common cause of pediatric stroke. Our patient presented with congenital cardiomyopathy (CCM), which may herald a neglected diagnosis, yet typically occurs in 20–30% of children undergoing corrective surgery (25, 26). Children with CCM develop a procoagulant state owing to tur -bulent blood flow, a malfunctioning hemostasis cascade (27–32), abnormal fibrinolysis factors (30–33), and anomalous platelet count and function (28, 30, 34, 35).

**Presentation/Diagnosis**

Primary restrictive cardiomyopathy examination commonly reveals evidence of pulmonary hypertension and cor pulmonale, such as loud P2, gallop, distended jugular veins, hepatomegaly, and ascites (36–38). Abnormal EKG findings (right and/or left atrial enlargement, though ST segment depression and ST-T wave abnormalities) are present to varying extent in 98% of cases (36).
Chest radiograph commonly shows cardiomegaly, particularly atrial enlargement, as well as pulmonary edema (36).

Up to 15% of children with PRCM present with arrhythmia (atrial flutter or atrial fibrillation), or conduction disorders (Mobitz 2 and third-degree AV block), or pre-excitation syndromes (e.g., Wolff–Parkinson–White syndrome) (38). Thereby, PRCM represents a known source of intracardiac thrombus formation due to blood stasis in the setting of severely dilated atrial chambers (18).

Although our patient did experience mild dyspnea on exertion, he did not exhibit other significant symptoms of cardiac decompensation, such as chest pain or syncope, and thus he remained undiagnosed until he developed symptoms secondary to his intracranial embolic stroke (36–38).

Primary restrictive cardiomyopathy is usually diagnosed by a combination of echocardiogram and cardiac catheterization, with the latter being the definitive test (18, 39–42). Elevation of biventricular end diastolic pressures in addition to pulmonary hypertension on cardiac catheterization is suggestive of PRCM (18, 39–42). Endomyocardial biopsy was non-diagnostic (18, 22, 43).

**State of the Art**

Adult acute arterial ischemic stroke management guidelines unequivocally support the use of IV r-tPA (44, 45), endovascular mechanical thrombectomy, or intra-arterial r-tPA administration (46, 47) in specific situations.

The Thrombolysis in Pediatric Stroke (TIPS) trial (9) and latest Royal College of Pediatrics and Child Health (RCPCH)
recommendations (48) represent the current landmark in acute pediatric stroke. Pediatricians remain cautiously optimistic in the light of adult thrombolysis therapeutic success. Despite substantial differences in thrombolytic pharmacokinetics and dose–response (49, 50), IV r-tPA in children can be deemed safe through a focus on meticulous selection criteria (9, 51). A majority of childhood strokes are due to intracranial arteriopathy, wherein mechanical thrombectomy is questionable, owing to the inflamed and friable arterial walls (52). Conversely, cardioembolic strokes represent an ideal correlate to adults that would benefit from mechanical intervention. However, the inability to use thrombo-aspiration devices due to small artery caliber and the consequent risk of thrombus fragmentation or migration may detract from enthusiasm.

While recent data have begun to unravel the detrimental effect of aging on collateral supply (53–55), pediatric collateral flow remains largely unexplored. Sparse reports compare pediatric stroke outcomes of similar NIHSS severity yet distinct collateral profiles treated with endovascular therapy (56). Nevertheless, the latest adult data support superior TICI scores (57–59) and functional outcomes (60–64) in patients undergoing recanalization in the setting of better collateral flow. Moreover, recanalization seems to carry fewer rates of hemorrhagic conversion post-instrumentation (57, 65, 66). At this time, the relationship of efficient pediatric cortical collaterals with diffusion/perfusion mismatch is incompletely understood. Unfavorable imaging does not render infarct progression an absolute certainty without treatment (67). Therefore, it would be intuitive to measure the recanalization benefit in clinical terms until radiological (i.e., angiographic) or parenchymal metrics are validated in children (68). In a field without studies controlled for intervention in the presence of good collaterals (69, 70), the preceding evidence informed the management of our patient.

With the aforementioned limitations to translate adult evidence to children in mind, we believe our case and others (71–77) provide hope and opportunity. Our child presented outside of the 4.5-h IV r-tPA window adopted by the TIPS trial methodology which represents the standard of practice in both children and adults. Additionally, the onset-puncture time was beyond our institutional guideline of 8 h yet within the current...
maximum advisory of 12 h by RCPCH. Nevertheless, the patient had a rich collateral supply, allowing for a small core infarct and large penumbra to be seen upon imaging, which led to our decision to intervene (Figure 1). Therefore, we pursued mechanical thrombectomy and salvaged a large ischemic brain area with a great impact on the child’s functional status. In terms of secondary prevention, we prescribed dabigatran which is a direct thrombin inhibitor that is independent of the variable antithrombin levels encountered in pediatrics and offers a favorable pharmacological profile (78). Primarily to avoid age-appropriate inconsistencies in daily intake, interactions with other medications, potential osteoporosis in long-term use of warfarin (79), and frequent laboratory monitoring (10, 80–82). Finally, our child underwent heart transplantation (18, 22, 39, 41, 42, 83, 84), which will prevent the occurrence of cardioembolic events.

CONCLUSION
Pediatric ischemic stroke is an under-recognized condition. We highlight stroke as a potentially devastating and treatable condition in children presenting with acute neurologic deficits. Owing to the possibility of sufficient collateral circulations and smaller core infarct volume, children might benefit from an extended therapeutic window for mechanical thrombectomy beyond 5 h.

INFORMED CONSENT
A written informed consent was obtained from the parents for the publication of this report.

AUTHOR CONTRIBUTIONS
AK conceptualized, drafted, and critically revised the manuscript. ED analyzed the data, critiqued, and revised the manuscript. JP acquired the data, critically reviewed, and revised the manuscript. VA reviewed the literature, analyzed the data, and critically revised the manuscript. SC reviewed the literature and critically revised the manuscript. OW, MR, and AH analyzed the data and critically revised the manuscript. CR-E conceptualized and outlined the manuscript, oversaw data acquisition, supervised the initial drafting, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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