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CASE REPORT

Modern endovascular treatments of occlusive pediatric acute ischemic strokes: case series and review of the literature

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Abstract
Purpose Literature on the endovascular treatment of occlusive acute ischemic stroke (AIS) in the pediatric population remains nebulous. Clinical trials evaluating the role of systemic and intra-arterial thrombolysis, and mechanical thrombectomy have been strictly isolated to the adult population and largely unknown in their safety and efficacy in the pediatric group.
Methods The authors present a review of the literature and their own two cases of occlusive acute ischemic stroke in children younger than the age of 10 years who were treated with modern endovascular devices, specifically with stent retrievers, and discuss their clinical and technical considerations as well as their limitations.
Results In both pediatric patients, a combination of stent retriever and Penumbra aspiration were used to achieve Thrombolysis In Cerebral Infarction (TICI) 2a or greater with reduction of overall stroke burden. A reduction of National Institutes of Health Stroke Scale (NIHSS) of 8 or greater was achieved at discharge. At 3-month follow-up, the patients had a NIHSS of 6 and 2, respectively. One patient continued to improve from NIHSS of 6 to 3 at 6 months.
Conclusion In carefully, selected pediatric patients, modern endovascular techniques may be used to treat occlusive pediatric AIS. However, larger clinical trials are needed to evaluate the overall safety and effectiveness.

Keywords Ischemic stroke · Pediatric · Endovascular · Thrombolysis · Thrombectomy

Introduction

The diagnosis and treatment of acute ischemic stroke (AIS) in children can be difficult given the diversity of underlying risk factors and lack of uniform treatment guidelines. Unlike adults, 55 % of strokes in children are ischemic as compared with 85 % in adult population. The etiology of childhood stroke varies greatly as compared with adults. Cerebral arteriopathies, sickle cell anemia, congenital heart disease, infections, and genetic/metabolic disorders are only some of the causative factors associated with childhood strokes.

High incidence of poor neurological outcomes associated with childhood AIS emphasizes the need for improved treatment modalities. The survival rate in children from stroke exceeds that of adult population, but more than half of the survivors are left with permanent neurological deficits. The average cost of childhood stroke treatment in the first year is approximately US$31,678 in the United States of America [1]. Long-term costs including rehabilitation and management of neurological disabilities can last for many years for the patient, the family, and the society.

In 2008, The American Heart Association Stroke Council outlined the guidelines for management of pediatric patients with acute ischemic stroke [2]. The use of intravenous (IV) tPA for thrombolysis for children with AIS is currently not recommended except in a clinical trial (Class III, Level of Evidence C). Two other guidelines stated that there is no evidence to support the use of thrombolytic therapies [3, 4]. Divergence among the published guidelines highlights the

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paucity of firm evidence base for uniform recommendations. Options for recanalization of occluded vessel outside of clinical trials are practically non-existent. Very limited options exist for the treatment of AIS in children, probably because of restricted guidelines and unknown efficacy and safety profiles of IV tPA and endovascular therapies.

In the current case reports, two children younger than the age of 10 years were treated using modern endovascular techniques to achieve recanalization during acute occlusive ischemic stroke. In particular, they were the youngest patients known in the literature to be treated using the Solitaire FR retrieval system (eV3-Corvidien, Irvine, California).

Illustrative cases

Case 1

A 9-year-old girl complained of headaches and deteriorated with sudden onset of right hemiparesis and aphasia. Her National Institutes of Health Stroke Scale (NIHSS) score was 9, and a magnetic resonance imaging (MRI) of the brain demonstrated early ischemic changes within the left frontal operculum (Fig. 1a). Coronal T2 image showed absence of flow void in the left middle cerebral artery (MCA) suggestive of an acute occlusion (Fig. 1b). The patient continued to deteriorate neurologically with a NIHSS of 16 despite IV tPA. An Alberta Stroke Program Early CT score (ASPECT score) of 8 was calculated from the post-tPA CT scan. Based on radiologic findings and clinical decline, the patient was considered for endovascular intervention.

Transfemoral cerebral angiography performed demonstrated a left internal carotid (IC) terminus occlusion just distal to the left fetal posterior cerebral artery (Fig. 1c, d). Multiple attempts using several 4 mm Solitaire FR stent retriever (Fig. 2a, b) and Penumbra aspiration system (Penumbra, Alameda, California) achieved a revascularization of Thrombolysis In Cerebral Infarction (TICI) 2a (Fig. 2c, d).

Post-operative MRI (Fig. 2e) showed infarction in the left basal ganglia and fronto-parietal territories. After optimal medical managing of the intracranial pressure ICP and brain oxygen, the patient was successfully extubated on post-procedure day 7. Trans-esophageal echocardiogram (TEE) revealed a moderate sized atrial septal defect measuring 1.5 cm with a continuous left to right shunt. No definite embolic etiology was found. She was subsequently discharged to rehabilitation on post-operative day 13.

Case 2

A 7-year-old boy diagnosed with mitral valve bacterial endocarditis (*Streptococcus Viridans*) was being treated with IV antibiotics for 1 week prior to present with an acute onset of left hemiplegia, dysarthria, and right-sided gaze preference. His NIHSS score was 17. CT of the brain demonstrated an ASPECT Score of 7 (Fig. 3a). CT angiography confirmed an occlusion of the right internal carotid artery (ICA) terminus and proximal M1 segment (Fig. 3b). A transthoracic

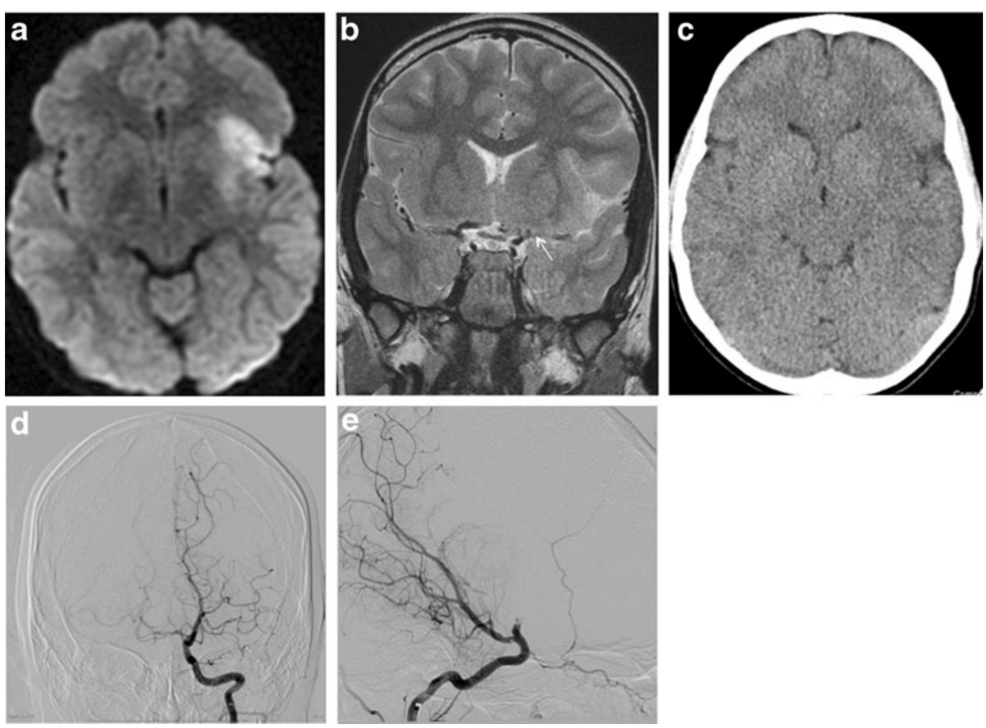

Fig. 1 In patient 1, **a** diffusion-weighted image of a MRI showed early ischemic changes in the left fronto-temporal lobe. **b** Absence of flow voids on the coronal T2 image suggestive of an acute occlusion in the left MCA (white arrow). CT head (**c**) demonstrated an ASPECT score of 8 with subtle hypodensity in the left frontal operculum. AP (**d**) and lateral (**e**) view of a left ICA injection demonstrated a carotid terminus occlusion

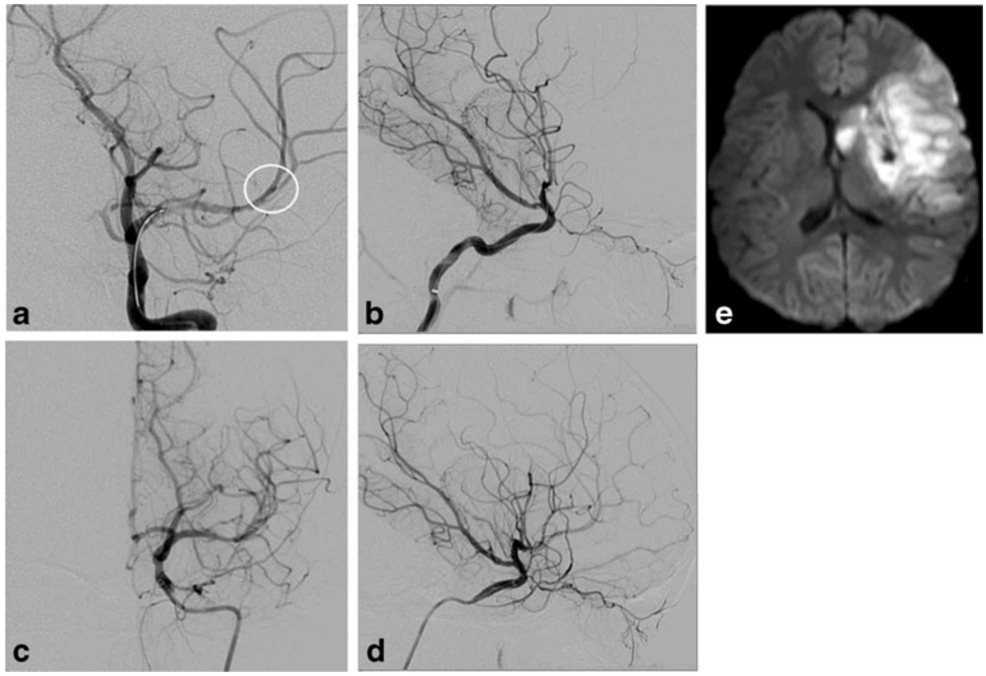

Fig. 2 In patient 1, AP (**a**) and lateral (**b**) view showed opacification of the posterior division of the left MCA with the Solitaire stent deployed. The distal tines can be seen deployed in the left M2 (*white circle*). Recanalization (TICI 2b) of the major large vessels with delayed MCA opacification can be visualized on the AP (**b**) and lateral (**d**) views of a left ICA injection. Post-procedural MRI showed diffuse restriction in the left fronto-parietal regions

echocardiogram (TTE) performed in the emergency department showed that the previously known echogenic calcified vegetation was no longer present. The patient was referred for endovascular intervention.

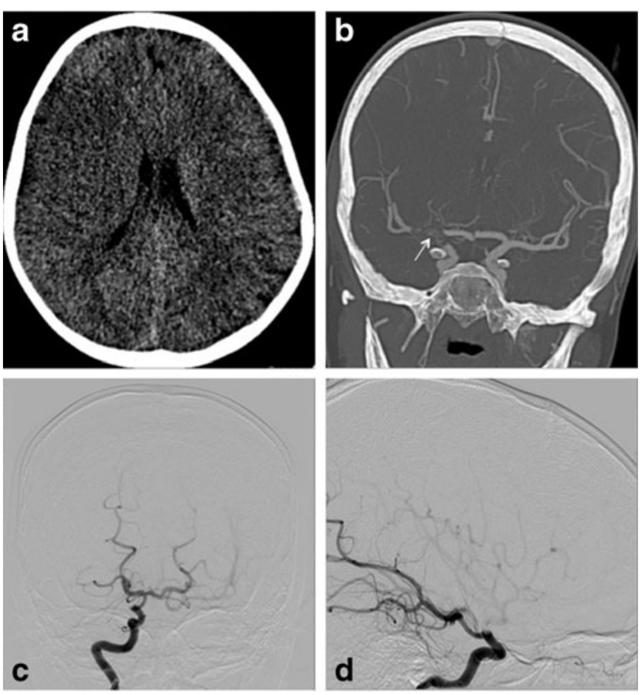

Fig. 3 In patient 2, CT head (**a**) with infarct window view showed subtle ischemic changes in the right frontal lobe. Coronal CTA (**b**) revealed a right carotid terminus occlusion (white arrow) extending into the left M1. AP (**c**) and lateral (**d**) view of a right ICA injection demonstrated a right carotid terminus occlusion just distal to the right posterior communicating artery

Transfemoral cerebral angiography confirmed a right carotid terminus occlusion just distal to the right posterior communicating artery. (Fig. 3c, d). Multiple attempts using the 4 mm Solitaire FR (Fig. 4a, b) failed, requiring the larger 6-mm Solitaire FR to achieve partial recanalization. Calcified thrombus was partially retrieved (Fig. 4c). In addition, balloon angioplasty (Fig. 4d–f) and Penumbra aspiration system were used to achieve a recanalization of TICI 2a (Fig. 5a, b).

An MRI of the brain (Fig. 5c) showed an infarction in the right frontal lobe consistent with occlusion of the superior division of the right middle cerebral artery. After optimal medical management of his ICP and brain oxygenation, the patient was successfully extubated on post-procedure day 6. The patient was transferred to rehabilitation on post-operative day 11.

Results

Thrombolysis In Cerebral Infarction 2a recanalization was achieved in both patients. No peri-procedural complications were noted. They were discharged to rehabilitation with a NIHSS of 8 with an overall decrease in NIHSS of 8 or greater. At 3-month follow-ups, the NIHSS was 6 and 2 for patient 1 and 2, respectively. At 6-month follow-ups, patient 1 continued to improve with an NIHSS of 3.

Discussion

Childhood stroke is a leading cause of morbidity and mortality with an incidence that ranges from 1.3 to 13 per 100,000 [5].

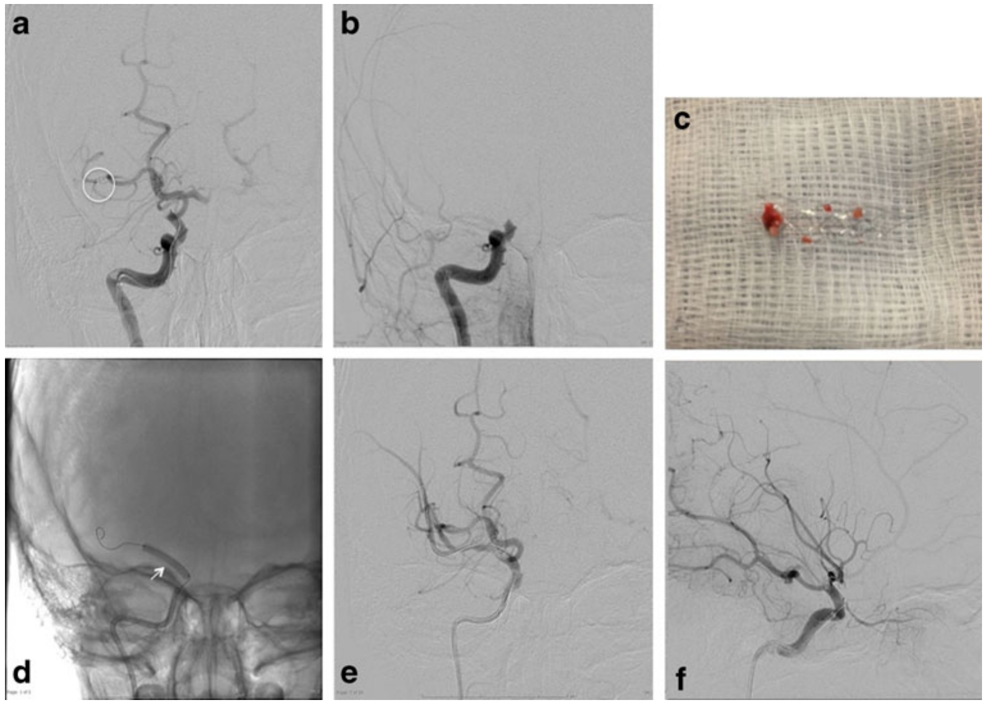

Fig. 4 In patient 2, AP (**a**) view showing the distal tines (*white circle*) of a Solitaire stent deployed in the distal right M1. Note the lack of the contrast opacification beyond the deployed stent. Post-Solitaire thrombectomy angiography (**b**) showed persistent occlusion despite retrieval of calcified thrombus (**c**) on the stent. A compliant NanoCross balloon is inflated (*white arrow*) in a subtracted AP view (**d**). Partial recanalization of the posterior division of the right MCA could be visualized on the AP (**e**) and lateral (**f**) view after post-balloon angioplasty

The mortality rate for childhood AIS is approximately 3–6 % with 70 % of the survivors debilitated with significant neurological deficits and carry a tremendous socioeconomic burden [6–8]. Very limited literature exists to guide the treatment of pediatric patients with acute intracranial vessel occlusion, and even few address any endovascular techniques.

The diagnosis and treatment of AIS are often delayed in children because of lack of physician awareness and the difficulty in differentiating an acute stroke from a wide range of stroke mimics (i.e. seizures, demyelination, and migraines). Unlike the adult counterpart, childhood stroke is far less common and less publicized in the literature and public campaigns. Several studies have shown that the average median time from symptom onset to diagnosis in childhood AIS ranges from 16 h to greater than 24 h [9–11]. In these studies, neuroimaging was also delayed, ranging from 8.8 to 16 h from symptom onset. Srinivasan et al. observed that physicians mentioned stroke as a possible diagnosis in only 26 % of the childhood AIS cases, despite the fact that 88 % of children presented with an acute focal neurological deficits [12]. Rafay et al. reported that stroke was suspected on initial assessment in only 38 % of pediatric population [11]. Lack of awareness leading to a delay in management is a major obstacle in the treatment of childhood AIS.

At most stroke centers, there is a lack of established protocol for timely diagnosis, imaging, and treatment for an acute intracranial vessel occlusion in pediatric patients, given its low incidence. Symptoms of childhood stroke can have a stuttering or progressive course, confounding stroke recognition, and proper triage. Stroke mimics occur more frequently compared with adult presentations. Headaches and seizures often accompany stroke onset in children, confounding the symptoms of AIS versus postictal paresis. Unlike the traditional risk factors associated with adult strokes (i.e. atherosclerosis, smoking, diabetes, and hypertension), the most common etiologies of childhood AIS are cerebral arteriopathies, which account for

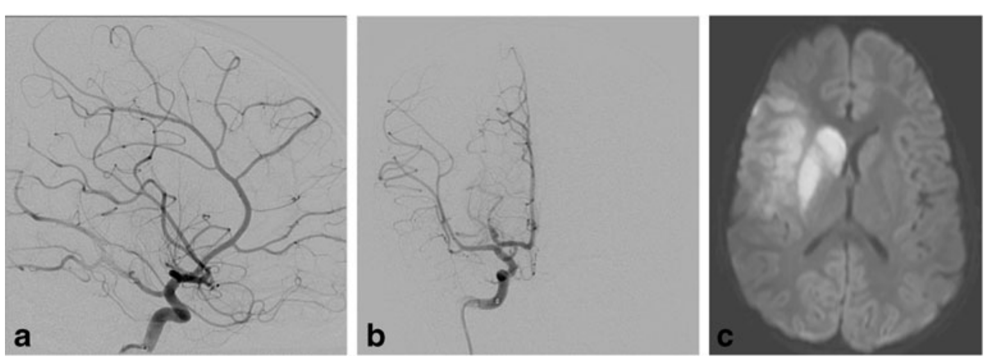

Fig. 5 AP (**a**) and lateral (**b**) view of a right ICA injection in patient 2 at the end of the procedure revealed recanalization of the major large vessels. The anterior division remained persistently occluded. Post-procedural MRI (**c**) showed diffusion-restriction in the right fronto-temporal territories

50–80 % of childhood AIS cases [7, 13, 14]. Significant infections such as varicella and meningitis are well-documented causes of pediatric strokes [15, 16]. There is a 5.01 odd ratio for the association of any infection (major or minor) with childhood AIS [17]. This presents a major challenge for physicians, given the high incidence of infections in this patient group. Other conditions such as moya moya disease or acute sickle cell crisis warrant other established, proven treatments and not systemic thrombolytics. Heterogeneous etiologies and diverse presentations are significant challenges in the diagnosis and treatment of pediatric strokes, limiting the potential for the administration of thrombolytics and endovascular therapies.

Neuroimaging provides additional challenges in diagnosis and treatment optimization. CT scan may not be the ideal imaging modality to diagnose childhood AIS. A study from a tertiary children's hospital found that childhood AIS was not visualized on CT scan in 62/74 (83.7 %) pediatric patients [12]. On the other hand, MRI provides greater sensitivity and specificity and is much more useful to distinguish between acute strokes from stroke mimics. However, 24-h availability of an appropriate team for urgent sedation as well as MRI scanner may be limited in most primary stroke centers.

The use of IV tPA for the treatment of ischemic stroke in children is not recommended by the current American Heart Association (AHA) guidelines except in a clinic trial [2]. The efficacy and safety of using alteplase in this group of patients remain ambiguous. The Thrombolysis in Pediatric Stroke (TIPS) trial has set forth to determine the safety and feasibility of IV thrombolysis in children with acute ischemic stroke [18]. Previous cohort studies such as The International Pediatric Stroke Study (IPSS) found that alteplase was given infrequently and at time intervals that deviated from the standard adult guidelines. Although there were no symptomatic intracranial hemorrhages, poor neurological outcomes were common in the study [19]. One of the barriers to administrate IV tPA in childhood stroke is the physiological differences in the coagulation and fibrinolytic parameters between children and adults [3, 20–22]. These differences may affect dose-related response and pharmacokinetics, when alteplase is used in children. Concentration of endogenous tissue plasminogen activator is lower, and plasminogen activator inhibitor Type 1 is higher in children than adults. This may imply decreased fibrinolytic function in children [21]. However, on a functional global assessment, there are some suggestions that fibrinolytic capacity in children is actually enhanced [20]. Because of these uncertainties, the optimal dose requirements to treat childhood AIS remains a mystery. For this reason, endovascular mechanical thrombectomy, although speculative, may provide a theoretical advantage over thrombolytics given that fibrinolysis is less relevant.

The current series is the first reported description of the applications and clinical outcomes of using both the 4-mm and the 6-mm Solitaire FR to treat occlusive pediatric AIS, especially in children younger than the age of 10 years. Literature on the use of efficacy and safety of modern endovascular techniques in children is scarce and lacks much needed prospective trials. The recent AHA guidelines published in January 2013 recommended Penumbra aspiration system and stent retrievers over other devices (Class 1, Level of Evidence A) in the treatment of adult AIS [23]. Extrapolating this to the treatment of childhood AIS can be difficult given the lack of safety and efficacy profiles on these devices in children and should only be considered on an individual case-by-case basis with an experienced multidisciplinary neurovascular team.

As endovascular devices and techniques for the treatment of adult AIS continue to evolve, their application in children continues to remain unknown except in a few case reports. The major endovascular stroke trials have so far excluded the pediatric population, thus limiting the understanding, safety, and outcomes of using these devices in this subgroup. Ellis et al. reviewed the literature and found a total of 34 cases of pediatric AIS treated with endovascular therapy [24]. Complete, incomplete, and absent recanalization was achieved in 12 (35.2 %), 13 (38.2 %), and 3 (8.8 %) cases, respectively. Hemorrhagic complications (peri-procedural and post-procedural) occurred in ten patients (29.4 %), although only one (2.9 %) was symptomatic. Only 11/34 patients underwent mechanical thrombectomy with only 1 (9 %) patient developing asymptomatic hemorrhage (IA tPA was also administered). Although the sample size is small, the complication rate is comparable to that from large, randomized trials in adults [25–27]. The remaining 23/34 received only IA thrombolysis, and 7 patients (30.4 %) developed intracranial hemorrhage. The higher hemorrhage rates associated with IA tPA may be secondary to the physiology differences in the coagulation and fibrinolytic pathways between children and adults. In addition, there was a delay in endovascular treatment given the mean time from onset of symptoms to endovascular therapy was 14 h, which is far beyond the typical interventional period in adults. Other case series in the literature have highlighted the utilization of endovascular devices (i.e. Balloon, Merci, Phenox, and Penumbra) in the pediatric stroke population with acceptable outcomes and without significant complications, although the safety profile and efficacy of each device has not been defined [28–31].

In the current cases, an aggressive approach was used in both patients and might draw some criticism. However, both pediatric patients would have qualified for endovascular rescue therapies had they been adults. In neurosurgical pediatric emergencies, surgeries are often performed beyond the indications for an adult (i.e. bilateral fixed and dilated pupils) because of patients' young age and potential for recovery and their "last chance of hope." Similar approach was undertaken with these patients with a thorough discussion with the patients' parents, who understood that these procedures were clearly outside the recommended guidelines. In case 1, the patient had clearly declined neurologically despite given IV tPA, suggesting progression of the thrombus formation into the ICA terminus as confirmed on DSA. In the second patient, the previous known vegetation had embolized into the right ICA terminus as evidently discovered on TTE. Without revascularizing the occluded vessels, both patients would have progressed to full MCA and anterior cerebral artery (ACA) infarcts, leading to life-threatening malignant edema and requiring a hemicraniectomy. Achieving a recanalization score of TICI 2a or greater conclusively reduced the stroke burden in both patients and postoperatively; they were successfully managed medically instead of requiring surgical decompression.

The two cases illustrated that Penumbra Aspiration System and Solitaire FR stent are complimentary devices for reperfusion strategy. Although this is purely speculative, it appeared that these devices are feasible to be utilized in the pediatric population based on the current cases and other published reports. The catheter maneuverability and stent delivery (even the 6-mm Solitaire stent) were smooth and without technical difficulties, partly due to the inherent non-tortuous anatomy of this subgroup. Although no peri-procedural complications from either device were observed, no conclusive statements could be made regarding their safety profile without a larger, clinical trial. Certainly, there were peri-procedural concerns especially using an oversized Solitaire stent (6 mm) in the second patient. Although the stent is larger, the flexibility and radial force did not appear to be potential challenges. Anecdotal experience from the treatment of adult MCA occlusion suggested that a larger stent retriever might achieve higher recanalization rate with increase radial force to engage the thrombus. The need for multiple devices and attempts during the procedures were probably the result of the inherent etiologies of stroke where embolic materials in these cases may be less amenable to stent capture, especially calcified thrombus. Recent publication of using the ADAPT technique in adult AIS with high success may be suitable to treat occlusive childhood AIS [32]. Since there is no device deployment with unforeseeable failures (i.e. breakage of stent retriever), this technique may be applicable to use in childhood AIS, provided that the occluded vessel can accommodate the larger catheters. The technological advancement to treat adult AIS continues to evolve, and their extrapolated applications in occlusive childhood AIS will also continue to be evaluated in individual cases. Nevertheless, the current Penumbra and the Solitaire devices are invaluable tools in the armamentarium of mechanical thrombectomy available to the endovascular surgeons.

To fully elucidate the safety and efficacy of these devices and techniques in the management of acute ischemic stroke in the pediatric population, the factors that differentiate it from adult stroke should be considered. Moreover, until dedicated, prospective pediatric trials occur, the use of these devices in children must be evaluated on a case-by-case basis with consideration of the endovascular surgeon's experience and comfort level.

Conclusion

Children presenting with an acute ischemic stroke with significant neurological deficits may be considered for endovascular therapy on an individual case-by-case basis at an experienced neurovascular facility. The current two cases of acute ischemic stroke in children treated with modern endovascular techniques highlights technical consideration and current limitations in the treatment the childhood AIS. Though no published clinical trials examining IV, IA, or endovascular mechanical thrombolytic strategies in children with AIS exist, improved reperfusion and outcomes can be attained in carefully, selected patients. Larger, randomized clinical trials are needed to define the optimal management of childhood AIS.

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