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Endovascular treatment of acute ischemic stroke in childhood: A comprehensive literature review based on the experience of a single center☆

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ABSTRACT

Acute ischemic stroke (AIS) in childhood is a relatively rare but significant condition that can result in long-term disabilities. There is a lack of standardized strategies for diagnosing and treating pediatric AIS due to limited evidence-based data on thrombolytic and endovascular treatments in children. This comprehensive literature review focuses on the experience of a single center in Italy and aims to highlight the main peculiarities of endovascular treatment (EVT) for AIS in childhood.

The review covers the diagnostic workup, the endovascular procedures, and the need for a specific thrombectomy program for pediatric AIS.

The review discusses the indications and considerations for thrombectomy in children, including the risk of complications and the challenges of extrapolating results from adult studies. The diagnostic protocols for pediatric AIS are also discussed, emphasizing the use of MRI to avoid X-ray and contrast medium exposure in children.

The combination of intravenous thrombolysis and mechanical thrombectomy has been examined, considering the differences between pediatric and adult thrombi. Technical considerations related to the size of pediatric patients are addressed, including the use of large bore catheters and potential concerns with access points.

The organization of a thrombectomy program for pediatric AIS is discussed, emphasizing the need for specialized facilities and expertise.

Although evidence for EVT in the pediatric population is based on case series, the importance of specialized centers and the lack of validated guidelines are evident.

1. Introduction

Acute ischemic stroke (AIS) is the first source of disabilities in Western industrialized countries [1,2]. It mainly affects adults, with a higher prevalence of elderly people. However, 1–7.9 out of every 100 000 children experience an AIS every year [3–5]; AIS in pediatric age is still an underdiagnosed entity with little clinical understanding. Regardless of age, irreversible neurological deficits are common consequences of AIS; despite pediatric cases being much less common than those in adults, the disability-adjusted life years (DALYs) after a pediatric stroke are much higher than after an adult case. Consequences may include intellectual disorders, behavioral issues, seizures, language disability, and sensory and movement disorders [2,6].

Even though AIS in children is uncommon, there are age-dependent singularities in risk factors, etiopathogenesis, clinical manifestations, and therapeutic strategies [7]. One obstacle to defining a standardized strategy for diagnosing and curing pediatric AIS is the paucity of validated evidence-based data about thrombolytic and endovascular treatments in children [8].

The classification of pediatric stroke based on age distinguishes

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strokes that occur between 28 weeks of pregnancy and 28 days after birth, which may be classified as perinatal strokes, and strokes that occur between 28 days and 18 years of age, which can be defined as childhood strokes [7].

The aim of this review is to highlight the main peculiarities of the endovascular treatment (EVT) of AIS in childhood ranging the diagnostic workup, through the endovascular procedure to the first days after EVT specifically to avoid recurrences, reviewing pre-existing evidences in the literature and correlating it with our experience.

2. General considerations regarding thrombectomy in pediatric age and indications

The effectiveness of mechanical thrombectomy within six hours for a proximal large vascular occlusion (LVO) was published in a series of five clinical trials in 2015 [9–13]. Nowadays, thrombectomy is the standard treatment for AIS in adults [14]. Notwithstanding the increased attention in pediatric MT, there is still little published research on the subject. Despite having a multicenter, retrospective design, the Save ChildS research, the largest study on pediatric MT, only included 73 pediatric LVOs [15]. The median age of patients in the Save ChildS Study was 11.3 years (IQR 7.0 – 15.0 and range 0.7 – 18.0 years), and the median time from onset to door was 3 h (IQR 1.5 – 5.0). The most common cause of stroke was cardioembolic (44 %), while in 37 % of patients the cause remained unknown. In 87 % of procedures, successful recanalization was achieved. Early clinical improvement was comparable to that observed in the HERMES meta-analysis of the adult population, and the long-term outcome (90-day mRS) was better in the pediatric population than in the adult population; an analysis by age group revealed the poorest outcomes in children aged 0–6 years.

2018 and 2019 AHA/ASA guidelines do not express any suggestion regarding thrombectomy in the pediatric population [16,17]. Only 2015 guidelines stated: “Endovascular therapy with stent retrievers may be reasonable for some patients < 18 years of age with acute ischemic stroke who have demonstrated large-vessel occlusion in whom treatment can be initiated (groin puncture) within 6 h of symptom onset, but the benefits are not established in this age group (Class IIb; Level of Evidence C)” [18]. As a result, the pediatric neurologists and neurointerventionists have to reach quick decisions on a treatment that has not been proven to be beneficial in children yet [19].

The child’s age, size, and the expected result in the absence of intervention are among the factors that are frequently considered. The frequency of mechanical thrombectomy in children is increasing, and case reports and small series have shown positive results, despite the absence of systematic efficacy and safety evidence. There are enough case reports, case series, and experiences to indicate that some children with LVO may benefit from mechanical thrombectomy. It’s also plausible that keeping patent arteries throughout the decades following a stroke has benefits that haven’t yet been discovered, as opposed to relying solely on collateral circulation. But there are important differences between adult and children AIS that can make it difficult to extrapolate adult results to children.

About 10 % of LVO in adults is thought to be caused by large artery atherosclerosis, with cardioembolic etiology being the most common. LVO in children has various and less-defined etiologies. Cerebral arteriopathies with secondary LVO may be prominent among children, as between one-third and half of all pediatric strokes are due to a cerebral arteriopathy. Although it is currently unknown how mechanical thrombectomy might affect arteriopathies with accompanying LVO, theoretically there is a higher risk of hemorrhage in a diseased artery during mechanical thrombectomy.

Focal cerebral arteriopathy (FCA), the most frequent pediatric non-atherosclerotic arteriopathy, needs specific considerations [20]. It is an inflammatory disease of the vessel wall, and VZV infection is very frequently associated. The indication for thrombectomy in known or suspected FCA is still debated; on the other hand, all studies on thrombectomy in the pediatric AIS include cases with FCA, and their results show no increase in the risk of intraprocedural complication, with a slightly lower rate of successful recanalization [15,21,22]. In our case series, we had two patients with FCA related to VZV, and in both cases we obtained a successful recanalization. However, one of them required a second EVT because of occlusion recurrence that was then treated by stenting of the occluded artery, with good long-term patency and clinical results.

Table 1
a comprehensive summary of the possible clinical presentations, with suspected etiology, diagnostic workup, and suggestions of endovascular treatment.

Clinical presentation	Suspected etiology	Diagnostic workup	EVT
Sudden onset, localizing symptoms, clinical history of cardiac or hematological pathologies	Cardioembolic stroke	MRI+MRA; CT if MRI not available; NECT, multiphase CTA, CTP if >4.5 h after onset	Thrombectomy as in adults if older than 5 y-o or taller than 110 cm. In younger children evaluate stent-retriever thrombectomy with smaller systems according to patient age and length.
Slow and fluctuating progression, no clear localizing symptoms, recent history of VZV infection	Non-atherosclerotic arteriopathy, FCA, moya-moya or moya-moya like	MRI + MRA, NECT if MRI not available; CSF sample (if possible)	DSA, if focal occlusion and not clear evidence of FCA → open a stent-retriever (than thrombectomy or stenting – according to the extension of the lesion in MRI). If non-focal stenosis or moya-moya no indication for urgent DSA
Slow and fluctuating or sudden onset, localizing symptoms, headache, history of trauma	Intracranial or extracranial dissection	MRI + MRA, NECT if MRI not available	DSA, if confirmed dissection start antiplatelet therapy (possibly by infusion). Bail-out stenting if no improvements with infusion of antiplatelets agents

Children’s cardioembolic AISs are generally caused by specific conditions. Stroke in children frequently coexists with other conditions such as sickle cell disease, congenital heart disease, and severe thrombophilia. They raise the risk of interventions, such as anesthetic and procedural-related thrombosis, as well as AIS. A retrospective large population study showed that children with either acquired or congenital cardiac illness had a 16.1-fold higher chance of developing AIS than children in general, with single ventricle physiology showing the highest frequency [23]. Four embolic AIS patients received thrombectomy at our facility; two had an MTHFR mutation, one had acute promyelocytic leukemia, and one case had no underlying prothrombotic disease.

Another frequently occurring cause of AIS in children is intracranial arterial dissection. However, most pediatric intracranial dissections occur without any prior trauma or a clear etiology. There is some data that suggests they may have an inflammatory substrate and that collagenopathies may also be the cause. In our experience treating adult patients with AIS, the majority of cerebral dissections can be treated with a Cangrelor infusion followed by conventional double antiplatelet treatment (DAPT). In our facility, only one case of pediatric AIS had intracranial arterial dissection and underwent EVT; in this case, stenting of the dissected artery was needed because the dissection extended and worsened despite DAPT (Table 1).

3. Choosing the right diagnostic protocol for stroke in children

Concerning diagnostic protocols, there is still uncertainty on what should be the preferred strategy, following the purpose of avoiding delays in the diagnosis of AIS in the pediatric population, still considering X-ray and iodinated contrast medium exposure in children and adolescents [24,25]. To avoid delays in the diagnosis of AIS in the pediatric population, CT and MR scanners should be easily available as well as the support of a pediatric neuroanesthesiologist considering that they require perfect collaboration from the patient which is hardly reachable in the pediatric ages. MRI is considered the diagnostic tool of choice in pediatric patients with AIS, because it may improve the detection of underlying pathologies such as stroke mimics or FCA, along with preventing X-rays and iodine contrast medium exposure. MR perfusion imaging could be performed with Arterial Spin Labeling (ASL) techniques that do not require a contrast medium injection. It has not been included in our fast-MR protocol, for time and technical concerns, but its potential benefit in patient selection in the emergency setup could be reconsidered in the future. Specific pediatric protocols for AIS should be set up in the MR scanners of pediatric emergency hospitals [26,27].

Nevertheless, susceptibility-weighted imaging proved to be equally accurate as perfusion imaging in estimating the extent of the ischemia [28]. According to a recent study, the ASL PWI-DWI mismatch ratio and the SWI-DWI mismatch ratio are equally effective in sizing the extension of acute ischemic stroke [29].

Moreover, considering the differences in AIS etiology between adults and children, the increased risk of complications, and the lower efficacy in pediatric arteriopathies if submitted to EVT, we should choose the diagnostic protocols even in the optic to rule out AISs related to cerebral arteriopathies if possible.

4. Combining IV thrombolysis and mechanical thrombectomy in children

TIPS (Thrombolysis in Pediatric Stroke) was a phase 1 clinical trial supported by the NIH to examine the pharmacokinetics and safety of intravenous tPA in children aged 2–18 within 4.5 h of AIS, if an arterial occlusion was identified by a MRI scan [30]. Despite the study's termination due to insufficient patient enrollment, in the absence of clinical trial data, it has been recommended that the adult dose of 0.9 mg/kg of body weight should be used when considering intravenous tPA in children. This would be a conservative dose because developmental differences in plasminogen levels may increase the effective dose for children [31].

Moreover, children's thrombi seem to be characterized by a more loosely woven fibrin structure than those in adults, according to in vitro data on the structure of thrombi made in the lab using plasma withdrawn by these two populations. These findings imply that thrombolytic therapy may, in theory, be more effective in children than in adults [32–34].

Delays in the diagnosis of AIS in children may prevent the use of IV thrombolysis in these patients but the recent evidence that expanded the therapeutic window in adults should be applied even to younger patients. On the other hand, MRI is more frequently used to diagnose AIS in children, and it improves the ability to see the ischemic tissue. The chance to increase the therapeutic window for IV thrombolysis in children employing a "tissue-window" strategy directed by advanced neuroimaging tools must be further investigated in new studies [35].

Current evidence supports the use of IV thrombolytics in adult candidates for mechanical thrombectomy [36]. On the base of what is known until now, a similar approach is indicated even in the pediatric population [37].

Despite what we reported above, in our experience of EVT for pediatric AIS, none of the patients received IV thrombolysis because all these patients arrived in our hospital out of the therapeutic window since they had an underhand onset or were secondarily transferred from other pediatric hospitals.

5. Technical considerations related to the size of the patients

Thrombectomy in adult AIS has two main different techniques using the direct aspiration of the cloth with large bore catheters or stent-retrievers, and neurointerventionists frequently combine the two techniques or shift between them if they do not achieve recanalization with their technique of choice. All EVT of AIS in adults are based on the use of large catheters, except in the case of distal medium vessel occlusions (MEVO), and, even in the case of MEVOs, large catheters are used to get the access to the cervical and proximal intracranial vessels.

Using such large catheters in children can induce some concerns.

Regarding the youngest age at which EVT can be taken into consideration, there is no agreement within the pediatric stroke community. A growing number of cases of successful thrombectomy in young children, including newborns under 1-year-old, indicate that it is sometimes safe and possible to perform it on them.

In our opinion the main concerns can come from the access point at the groin in children below 4 years of age. In these patients a 4 French introducer sheath is recommended, but studies have showed that the main indicator of the femoral artery diameter is the weight of the patient [38,39]. Another study showed that patient height was the best predictor of FA diameter, and an increase of 10 cm in patient height corresponded to an approximately 0.5 mm increase in FA diameter [40]. No clinical or radiologic spasm was related to a mean artery-to-catheter difference percentage of 58.9 % or higher, calculated as (artery - catheter)/artery* 100 [41]. Extrapolating data from the literature, we can say that a child over 5 years and 110 cm in length has a low risk of femoral access complications using an 8 F femoral sheath as in an adult. Choosing the diameter of the femoral sheath, and consequently all the endovascular system, we must remember that the size of the sheath refers to its inner diameter; therefore, the outer diameter of the sheath should always be checked in pediatric cases. Radial access sheaths have usually thinner walls than femoral, and they should be considered in pediatric cases even for femoral access.

Regarding the use of large bore catheters and stent-retrievers in the cerebral vessels, the diameter of the craniocervical district reaches 94 % of the caliber in adults at the age of 5 years; therefore, we can think of patients over the age of five as having vessels that are comparable to those of adults from a size viewpoint. Most adult endovascular devices are compatible with artery diameters beyond the age of five [42,43]. Despite that, we must remember that vessels in children are still more prone to vasospasm, so smaller guide catheters may be required to reduce the danger of vasospasm. Considering the concerns of deploying stents in the intracranial vessels, the limited experiences reported show that the procedure is safe even in long-term follow-up [44,45]. When forecasting the diameters of cervicocerebral vessels in children, BMI may not offer any further information beyond age.

There is no evidence regarding the safety and efficacy of the different thrombectomy techniques. Good results have been reported with either stent-retrievers and direct aspiration [37,46,47]. Notably, the investigators of Save Childs performed a secondary analysis comparing the recanalization rates and functional outcomes associated with various thrombectomy techniques and devices across age groups. There was no difference in the incidence of complications by age group. In pediatric patients, they did not observe a difference in recanalization rates between first-line contact aspiration and first-line stent retrievers. The clinical outcome was comparable across all treatment groups. However, they observed a greater incidence of complications when a stent-retriever was utilized as opposed to the contact aspiration technique [48].

If an aspiration technique is used, it is important to limit blood loss

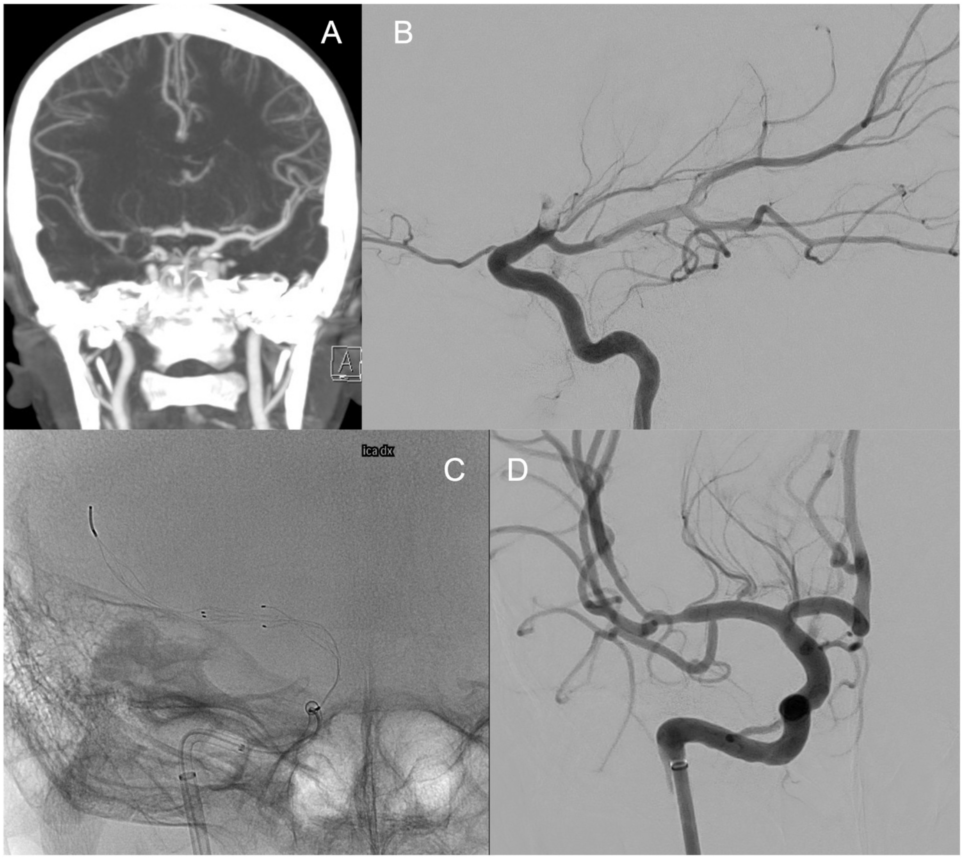

Fig. 1. *: A: a CTA MIP coronal reconstruction* showing the occlusion of the distal segment of the intracranial internal carotid artery with good collaterals. B the occlusion as shown by the DSA in lateral projection. C: a combined technique with stent-retriever and a aspiration catheter was used. D: the result of the thrombectomy with complete recanalization.

during aspiration. Given their smaller blood volumes than adults, children may have higher potential blood loss as a percentage of total blood volume from aspiration, and severe blood loss may worsen cerebral ischemia.Fig. 1.

6. Organization of the thrombectomy program for children AIS

Frequently, the emergency system for pediatric patients is less organized than for adults, and pediatric hospitals are often not equipped with 24/7 neurointerventional facilities [49]. Specific pediatric protocols should be set in both the CT and MR scanner and the angiographic suite to reduce the dose maintaining the standard quality of the images. CT scanners should be equipped with automatic injectors that allow the injections of very small quantities of contrast media.

The prompt availability 24/7 of all the required competencies is mandatory when treating a pediatric stroke. The pediatric stroke neurologist along with the general pediatrician are the pivot in the management of these cases; the pediatric neurointensivist/anesthesiologist is also one of the main actors in the management of pediatric AIS during the diagnostic workup, EVT and in the hours following the treatment with the goal of stabilizing the homeostasis of the children. The neurointerventionist should have experience in the treatment of both adult AIS and pediatric pathologies [7,24]. In our experience, GA is preferable compared to CS in the EVT of pediatric AIS. In our center, most of the EVTs for adult AISs are conducted under CS, but in pediatric cases GA is preferred, because it allows superior comfort to the patients, and we can obtain perfect immobility that is of high value when we need a deep understanding of the underlying pathology (i.e. to acquire high-resolution cone beam CTs that allows high-quality visualization of intracranial stenosis and dissections) and of the results of our treatment, allowing to reduce contrast media and radiation administration. Moreover, endovascular maneuvers in small pediatric arteries are safer in GA. Besides the pediatric stroke neurologist, the general pediatrician, the pediatric neurointensivist, and the neuroradiologist, other competencies that should be involved are hematologist, immunologist, and geneticist [24].

7. Conclusions

Despite the huge advances obtained during the last years in the treatment of adult AIS, when we face a case of pediatric ischemic stroke, we must consider specific distinctive features between children and adults that provide remarkably insightful clues for the diagnosis and treatment. The high incidence of atypical presentations without localizing symptoms could induce delays in the diagnosis. Etiopathogenesis of ischemic stroke in the pediatric population is different from adults and can lead to different therapeutic strategies. Evidence of the safety and the efficacy of EVT in the pediatric population comes from case series, and the results of a randomized controlled trial are lacking (considering the wide heterogeneity of pediatric ischemic stroke, a trial is very difficult to be designed and conducted); this reflects the absence of validated guidelines and the need of treatment in highly specialized centres.

CRediT authorship contribution statement

Guglielmo Pero: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Francesco Ruggieri:** Writing & editing the text, Formal analysis, Data curation, Conceptualization **Antonio Macera:**

Validation, Supervision, Investigation. **Mariangela Piano:** Validation, Methodology. **Cristina Motto:** Validation, Formal analysis. **Amedeo Cervo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Arturo Chieregato:** Validation, Supervision, Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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