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Pediatrics in South America (L Landry and WB de Carvalho, Section Editors)

Arterial Ischemic Stroke in Childhood

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Abstract

Purpose of review Arterial ischemic stroke in children is a severe disorder with significant morbidity and mortality. Urgent diagnosis is mandatory in order to save lives or minimize neurological sequelae. However, recognition of stroke in children is more difficult than in adults. Barriers such as low suspicion, diverse risk factors, difficulties performing neuroimages, and a lack of protocols for diagnosis and treatment make stroke management in children a challenge. This article aims to review the approach to arterial stroke in children.

Recent findings Recently, more focus has been placed in the development of comprehensive stroke centers for treatment of stroke in children. Shortening time for diagnosis allows initiating a prompt and successful hyperacute treatment. Neuroprotection must be initiated before diagnosis confirmation. As in adult patients, widening the thrombolytic treatment time window and optimizing secondary stroke prevention are main points to develop. Early decompressive hemicraniectomy in children with malignant infarct should

be considered.
Summary A multidisciplinary team is necessary for the diagnosis and treatment of children with brain attack. A particular "stroke code" must be established in each institution for stroke management and evidence-based guidelines should be developed.

Introduction

Stroke is increasingly recognized as an important childhood disorder, with an incidence between 2 and 13 per 100.000 children per year, similar to that of pediatric brain tumors [1].

Incidence varies by age and sex; it is highest in infants and children aged < 5 years and higher in boys than in girls. Ischemic stroke ratio in newborns is almost 6 times greater than in older children [2••].

Stroke is one of the ten most common causes of death in children and three-quarters of survivors have sequelae [3].

Arterial ischemic stroke (AIS) occurs due to interruption of arterial blood flow to the brain.

The thrombo-occlusive event may be due to a remote source of embolism such as congenital or acquired heart disease (CHD/AHD) and neck vessels, or an in situ thrombosis related to an arterial wall abnormality, or even congenital/acquired prothrombotic conditions.

Risk factors for stroke are different in children than in adults. Atherosclerosis or smoking in childhood is a very infrequent risk factor.

With the advent of advanced neuroimaging techniques and increased awareness, the diagnosis of stroke in children has become commoner.

Recent acute and preventive treatment recommendations are based on interventions that are effective in adults, rather than on data regarding efficacy in children [4]. However, hyperacute AIS treatments that limit ischemic brain injury may be applicable to all age groups. Primary preventive measures aimed to avoid the first stroke and secondary prevention of recurrence should be targeted to underlying risk factors.

Clinical presentation

Arterial ischemic stroke in childhood usually presents with focal neurological symptoms, with or without headache, such as hemiparesis, hemisensory deficit, visual field deficit, aphasia, facial weakness, other cranial nerve deficits, and unilateral ataxia. Focal seizures are frequent.

In infants with presumed perinatal ischemic stroke, an emerging hemiparesis, often manifested as early hand dominance, is diagnosed after the neonatal period. Neuroimaging findings show remote ischemia in a vascular distribution, presumed to have occurred during the perinatal period [5].

It is important to recognize other neurological disorders that may mimic stroke in children. These include postictal focal weakness (Todd's paralysis), hemiplegic/complicated migraine, reversible posterior leukoencephalopathy syndrome (RPLS), acute demyelination, tumors, hypoglycemia, and occasionally psychogenic/conversion disorder [6, 7]. For that reason, AIS should be included in the differential diagnosis of every child with an acute onset of focal neurological deficit.

Risk factors

Approximately 50–80% of children with AIS have at least one identifiable risk factor for stroke. Arteriopathies and congenital heart disease (CHD) are associated with 50% and 20–25%, respectively, of AIS in children in developed countries [8].

Sickle cell disease (SCD) is a very common cause of pediatric stroke in many countries but not in Argentina [9].

The patient's age at stroke onset could contribute to the finding of etiology and risk factors.

In older children with AIS, infections even banal, head/neck trauma, manipulation, CHD, dehydration, systemic diseases (hepatic, renal, gastrointestinal, hematologic), and rheumatologic conditions should be ruled out. Cerebral vasculopathy should be considered if dysmorphic features, neurocutaneous markers, and connective tissue disorders are present.

The extent of contribution of acquired inherited prothrombotic disorders remains under debate. An important meta-analysis showed a significant association between first AIS and protein C or antithrombin deficiencies: factor V G1691A, factor II G20210A, homozygous thermolabile methylene tetrahydrofolate (MTHFR) mutations, lipoprotein (A) high levels, and the presence of antiphospholipid antibodies [10].

Inherited metabolic diseases can cause acute focal neurological deficits and stroke-like episodes [11]. In case of radiological evidence of infarction, not confined to a known vascular territory, metabolic causes may be considered. For example, homocystinuria has been associated with increased thromboembolic events due to direct endothelial dysfunction [12]. Other metabolic disorders with known increased risk of stroke include Fabrys disease, Menkes disease, mitochondrial encephalopathies, organic acidemias, and urea cycle defects. The International Pediatric Stroke Study published a prospective study for the prevalence of risk factors for AIS [8]. The prevalence of various risk factors varied by age group; arteriopathy was most common in children aged 5 to 9 years, acute systemic conditions were more common in younger children, and chronic head and neck disorders were common in older children.

Infarcts were most commonly located in the anterior circulation, probably related to the high prevalence of arteriopathy in the anterior circulation [13]. Cardiac disease was identified in almost 1/3 of patients. Older age at time of surgery, cardiopulmonary bypass, and need for reoperation have previously been shown to be associated with increased risk of perioperative AIS [14]. Arteriopathies due to infection in children are emerging. The association with varicella has been previously described, but other pathogens are also likely to play a role.

Prothrombotic states were reported in 13% of children with AIS [8].

Special consideration of risk factors in pediatric stroke

Cervical arterial dissection

Both the internal carotid artery (ICA) and vertebral artery (VA) in the neck and skull base have the potential to sustain dissection. This can occur either in association with major or trivial trauma and sometimes spontaneously.

Cervical arterial dissection is an under-recognized cause of AIS in children, particularly in the VA at C1–C2 vertebral junction. Spontaneous dissections may be secondary to underlying collagen abnormalities such as Ehlers-Danlos or Marfan syndromes. Symptoms of dissection depend on infarct location and include cranial nerve, motor, sensory, visual, or cerebellar signs/symptoms. Acute severe headache and neck pain are reported at presentation. The underlying mechanism of stroke is endothelial injury, tearing, and separation between intima/media or media/adventitia causing exposure to collagen, activated tissue, and von Willebrand factors leading to thrombus formation. This can cause occlusion or artery-to-artery embolism. Pseudoaneurysm may develop secondary to impaired integrity of the vessel wall and persistent arterial occlusion. The risk of recurrent stroke or transient ischemic attack (TIA) in children with dissection is around 12% and can occur up to a few years post-initial presentation [15].

Moyamoya arteriopathy

Moyamoya is characterized by progressive stenosis and occlusion of terminal internal carotid artery (ICA) with collateral formation starting at the circle of Willis (hypertrophied basal ganglia perforators arteries) that eventually spread to the rest of the intracranial circulation [16].

Pediatric moyamoya tends to be mainly ischemic. When moyamoya occurs in isolation, it is termed as "disease" and when it occurs in presence of an identifiable risk factor (i.e., neurofibromatosis type-I, SCD, Trisomy 21, and other genetic syndromes), it is termed a "syndrome." Patients with moyamoya present with recurrent "migraine-like" vascular headaches, recurrent TIA (often hyperventilation-induced), stroke, cognitive decline, and seizures (20–30%) [17].

Bacterial infections

AIS can occur as a complication of central nervous system infections, particularly pneumococcal and tuberculous meningitis. Neuroimaging to rule out infarction should be performed in every children with proven or suspected meningitis who develop sudden acute focal deficits/seizures.

AIS is reported in 13–35% on computed tomography (CT) and 57% on magnetic resonance imaging (MRI) in tuberculous meningitis [18]. Due to the extensive infectious involvement of the basal cisterns in tuberculous meningitis, there is exudative encasement of the circle of Willis causing arteritis, stenosis, or vasospasm. This may progress to full arterial occlusion resulting in AIS that can be recurrent and multifocal, involving both the anterior and posterior circulations in small or large territories.

Viral infections

The most common viral infection associated with AIS is varicella zoster virus (VZV). There is evidence that VZV can infect the walls of the cerebral arteries, especially the terminal ICA, proximal anterior cerebral artery (ACA), and proximal middle cerebral artery (MCA), which are innervated by branches of the trigeminal nerve. Spread of VZV along these nerves following reactivation of the

latent virus in the trigeminal ganglion has been documented and viral invasion of the implicated arterial segments results in an inflammatory response [19]. Post-varicella stroke is a well-described entity and is now considered part of a wider spectrum of post-infectious stroke syndromes called transient cerebral arteriopathy (TCA). The presentation is acute hemiparesis and/or aphasia caused by infarction of the basal ganglia with a unifocal area of stenosis/occlusion at the bifurcation of the ICA. A history of preceding VZV infection is present in approximately 15–20% of TCA cases [20]. This arteriopathy typically follows a monophasic course lasting 3–6 months, beyond which further disease progression (new vascular involvement) should not occur. However, recurrence of AIS or transitory ischemia attacks (TIAs) is still possible within this initial course.

Other infectious agents implicated with TCA are the following: parvovirus B19, cytomegalovirus, mycoplasma pneumoniae, Borrelia burgdorferi, enterovirus, and helicobacter pylori [21].

Heart and AIS

Cardiac causes of AIS are found in up to 20–25% of children with AIS secondary to emboli either from the heart (i.e., cardiomyopathy, myocarditis, valvular disease) or from a systemic venous clot when a right-to-left shunt from a septal defect as patent foramen ovale is present. Occasionally, it can be procedure-related secondary to cardiac surgery or catheterization [14].

Thrombophilia

Thrombophilia is a risk factor for incident stroke. However, its impact on outcome and recurrence needs to be further investigated [22].

Diagnosis

The goal of acute stroke management is to stabilize the patient and complete the initial assessment including imaging and laboratory studies, within 60 min of patient arrival [2••].

Early recognition

Delay in recognition of pediatric stroke is nearly 24 h after onset, and it occurs primarily in health centers [23].

Early recognition of ischemic stroke may be facilitated by the use of screening protocols for detection of signs and symptoms in the emergency department. Age-modified stroke recognition tools have been proposed, but require further development and validation [24, 25].

In order to improve communication between health care staff members, a "stroke code" should be implemented.

Initial diagnosis approach

This primary evaluation includes the following: neuroimaging, with appreciation of the intra- and extracranial vessels; cardiology assessment; thrombophilia tests; and blood inflammatory markers.

Imaging approach

Due to the difficulties in making a clinical diagnosis of pediatric stroke, neuroimaging has become an essential part of the assessment in these patients.

It is important to rule out the main differential diagnosis as complex migraine, RPLS, demyelinating diseases, and tumors, among others [26••].

Computed tomography

In our institution, mostly because of logistic issues, the use of non-contrast CT followed by cervico-cephalic CT angiography is the first choice in children suspected of having an acute stroke.

We consider that, in this particular clinical setting, the potential information that this images may provide overcome the concerns about the use of radiation and iodinated contrast media.

Moreover, CT imaging is more accessible, simpler, and faster than MRI. It generally does not require sedation and is also extremely sensitive for detecting acute hemorrhage. This is especially relevant since half of the strokes in children are hemorrhagic [1].

Conventional CT performed in the acute setting (less than 6 h from clinical onset) can be normal and does not exclude ischemia. Even though, it may reveal early signs, especially in MCA territory.

CT angiography is extremely sensitive in depicting arteriopathy signs which accounts for up to half of children with AIS [8, 27]. It can easily reveal middle and large arterial vessel occlusions, mural irregularities, double lumen, and other signs that may suggest the underlying pathophysiology as embolism, dissection, or vasculitis.

Eventually, the performance of delayed scans may provide important information about collateral circulation.

Magnetic resonance imaging

MRI can be the first choice in those institutions that have the logistic capability of performing it in the acute phase or, as it is the practice in our center, a second technique after CT imaging.

Compared with CT imaging, MRI offers a better definition of the acute ischemic core by showing areas of parenchymal restriction on diffusion weighted imaging (DWI) which is relevant for differential diagnosis, accounting that from 20% to more than 50% of children presenting to the emergency room with stroke-like symptoms may have stroke-mimics [6, 28••, 29].

It may also demonstrate a potential operational penumbra when it is supplemented with angiography and an enhanced or non-enhanced perfusion sequence pseudocontinuous arterial spin labeling (pcASL).

Moreover, by the use of susceptibility-weighted imaging (SWI) or T2 gradient echo images (T2*-GRE), it is possible to detect hemorrhage with acceptable sensitivity.

A rapid stroke protocol consisting of fluid-attenuated inversion recovery (FLAIR), DWI, apparent diffusion coefficient (ADC), T2-GRE, MRA, and perfusion (pcASL) can be done in about 20 min.

The drawbacks of this approach, besides the need for anesthesia, are the non-stroke causes of DWI restriction such as abscess, some acute demyelinating lesions, certain tumors, and some stages of hemorrhage, among others.

In recent years, the incorporation of vessel wall images (VWI) has increased diagnostic sensitivity for arteriopathy (see Fig. 1).

By the recognition of different patterns of wall enhancement on black blood sequence, it is possible to recognize vasculitis and dissections.

Neck vessels Doppler ultrasound

Extracranial vessel imaging should be immediately performed to determine dissection or pseudoaneurysm presence [2••].

.Cardiological approach

Performing a transthoracic echocardiogram is indicated when intracardiac thrombi or vegetations are suspected, as well as to diagnose intracardiac right-to-left shunts [30, 31•, 32, 33••].

Intraesophageal echocardiography is indicated if the transthoracic echocardiogram does not depict pathology, especially if located in the left atrium [2••, 30, 33••].

Electrocardiogram arrhythmia screening and Holter monitoring are peremptory until the cause of the stroke is found [2••].

Laboratory approach

Immediately upon admission, different aspects of the patient's condition must be checked by performing a complete blood count, erythrocyte sedimentation rate, and basic biochemistry: urea, creatinine, electrolytes, glucose, acid-base status, lactate, and basic coagulation tests [2••, 31•, 32, 33••]. Toxicological causes should be rule out.

Further laboratory tests should be performed according to the etiological suspicion, child's semiology, and treatment options.

Based on the diagnostic orientation, serology is to be performed searching for VZV, herpes simplex, mycoplasma, enterovirus, and borreliosis. If

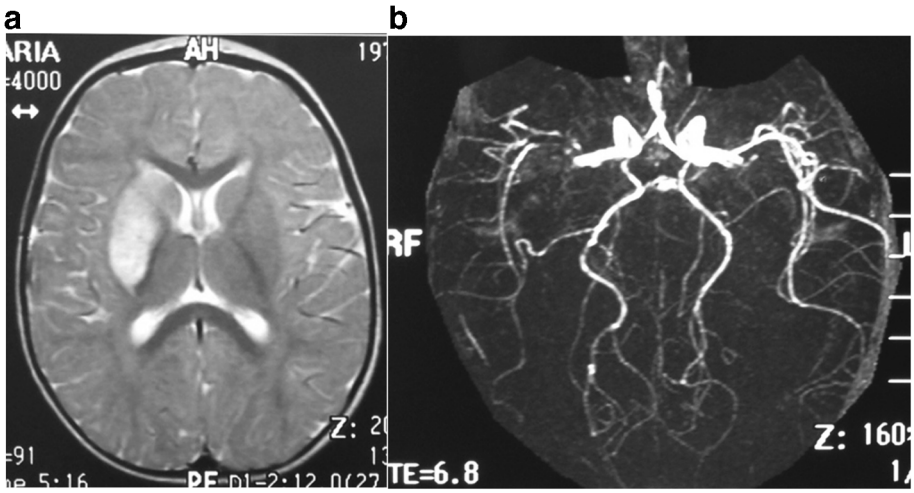

Fig. 1. Transient cerebral arteriopathy. Eight-year-old boy with recent history of chicken pox who was admitted to our institution with an evolution of 24 h of headache and oscillating left hemiparesis. **a** MR-Axial T2-WI: There is a hyperintense lesion involving the right striatocapsular region that fits the deep territory of the middle cerebral artery (MCA). **b** MRA-TOF 3-D: shows irregular signal loss in the proximal segment of the right MCA with poor distal flow.

inflammatory vasculitis is suspected, screening for anti-core antibodies, antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies (ANCA) is indicated [2••, 31•, 33••].

If there is any suspicion of metabolic diseases, amino acids, homocysteine blood level, and organic acid screening in urine should be requested [1, 2••, 31•, 32].

.Since risk factors are multiple and can coexist, thrombophilia testing is indicated including proteins S and C, antithrombin, lipid profile, lipoprotein A, factor V Leiden, prothrombin G20210A mutation, MTHRF mutation, and antiphospholipid antibodies [22, 31•, 32, 33••].

Performing a lumbar puncture should be considered in children with arteriopathy of unknown origin, meningitis, or encephalitis suspicion [31•].

Stroke severity score

The National Institutes of Health Stroke Scale (NIHSS) is a reliable quantitative measure of acute stroke severity in adults and predicts stroke outcome at 7 and 90 days. The adult NIHSS is the primary examination used for adult stroke research and acute treatment trials [34].

The pediatric scale (PedNIHSS) was developed by a panel of pediatric and adult stroke experts by a consensus review process in which each item of the NIHSS was modified for age-dependent variations in comprehension and participation in the exam item and age-appropriateness of testing materials (language items, picture, commands). All items were adapted to an age-appropriate format, while the scoring strategy and scoring ranges for all items administered in the adult NIHSS were taken in the PedNIHSS [35].

The PedNIHSS has the same examination elements as the adult scale including 11 neurological domains and 15 scored items. The total score for the PedNIHSS ranges from 0 (least severe) to 42 (most severe).

The PedNIHSS is a quantitative score that measures the neurological deficit related to the acute ischemic event in order to facilitate communication between emergency physicians and consulting neurologists. It is also a baseline score for predicting stroke outcomes.

Hyperacute treatment

It is urgent "to rescue the penumbra area," that is, the tissue that surrounds the focus of ischemia that has not yet died but that can do so if the blood flow is not recovered.

Neuroprotection must be started even when the stroke has not been confirmed, since the entities known as stroke mimics may also imply severe brain damage. Recommendations concerning stroke in childhood are mostly drawn from adult patient guidelines and based in consensus and opinions of pediatric experts [2••, 31•, 32, 33••, 36••, 37••, 38•].

There is no evidence based in controlled and randomized studies in children.

Monitoring and support therapy approach

Children with ischemic stroke should be monitored in an intensive care unit for at least 48–72 h after the acute event, because neuroprotective and eventual neurocritical supportive care should be administered in that setting [2••, 31•, 36••].

Blood pressure, temperature, oxygen saturation, and heart and respiratory rate monitoring must be indicated in every children with a clinical diagnosis of stroke.

A patent airway and a stable venous line must be maintained. Oxygen saturations should be kept ≥ 92% [2••, 32, 36••, 38•].

Patient intubation and ventilation should be considered if Glasgow Coma Scale (GCS) ≤ 8, child's airway is not protected, or intracranial hypertension is present [36••].

The head should be placed horizontally to the plane of the bed for at least 24 h and for up to 72 h as tolerated. Oral intake should be withheld until swallowing is considered safe [2••, 33••, 36••].

Neuroprotection is based on prevention, so hypertension, hyperpyrexia, hyperglycemia, and seizures, as well as other aggressive factors that can worsen the perfusion in the penumbra area, should be monitored and avoided.

Hypertension

In a retrospective children study, Brush et al. detected at least one hypertension episode during the acute phase of strokes in 60% of patients. Two-thirds of children with stroke presented arterial hypertension in the first 24 h of onset and 20% during the first 3 days, mainly in patients with heart disease, moyamoya, and occlusive vasculopathy [39].

Transient systemic hypertension can be attributed to a compensatory mechanism trying to protect cerebral perfusion and it usually normalizes within 24 h after the event.

Lowering systolic blood pressure (SBP) should be done cautiously and with close monitoring since it may turn into a major neurological deterioration. ASA/AHA adult guidelines recommend lowering high hypertension values no more than 15% in the first 24 h [38•].

High and persistent blood pressure levels in the first few days may indicate the onset of malignant cerebral edema, hemorrhagic transformation of the infarct, or heart or kidney disease [40].

Unlike Grelli et al., Adil et al. found systemic arterial hypertension in children with AIS was associated with increased hospitalization time and mortality [41, 42].

Optimum blood pressure in children with ischemic stroke has not been established [43].

Recent guidelines propose that hypertension must be treated in those patients whose SBP exceeds 95th percentile for age by more than 15% and for more than 1 h, but always if it exceeds 20% of 95th percentile [33••, 37••].

Hyperpyrexia

Fever must be prevented and treated in order to avoid increasing cerebral metabolic demand. Acetaminophen is recommended in adults with acute

stroke and fever. Cooling blankets are also used [38•]. This recommendation is extrapolated to children [2••, 33••, 37••].

The Prasad K et al. meta-analysis demonstrates an increased risk for short-term mortality in adults diagnosed with AIS and hyperthermia [44]. In contrast, Grelli et al. showed in children that temperature ≥ 38° was not a poor neurological outcome prognostic factor after 3 months [42].

Hyperglycemia

Hyperglycemia is cause of increased ischemia and cerebral edema, while hypoglycemia can cause seizures. Grelli et al. found that glycemia of ≥ 200 mg/dL was independently associated with worse Pediatric Stroke Outcome Measure [33••, 42]. Rivkin et al. recommend not to infuse glucose into intravenous fluids for children age ≥ 2 years old unless hypoglycemia was present [37••].

Extensive studies found a relationship between hyperglycemia and poor evolution in adults with cerebral ischemia [45–47].

Seizures

AHA/ASA recommends not using prophylaxis with anticonvulsant therapy in children with AIS, unless in cases of MCA thrombosis. Prolonged electroencephalogram monitoring should be considered to detect subclinical seizures. Seizures also may indicate a hemorrhagic transformation of the infarct [2••, 32, 33••].

Endovascular reperfusion therapy

Endovascular reperfusion for AIS is a treatment to restore blood flow to the brain. It is carried out by mechanical thrombectomy (MT) or an intra-arterial fibrinolysis.

Mechanical thrombectomy

MT is an endovascular procedure consisting in removing a thrombus occluding cerebral arteries by aspiration or by a stent retriever (see Fig. 2).

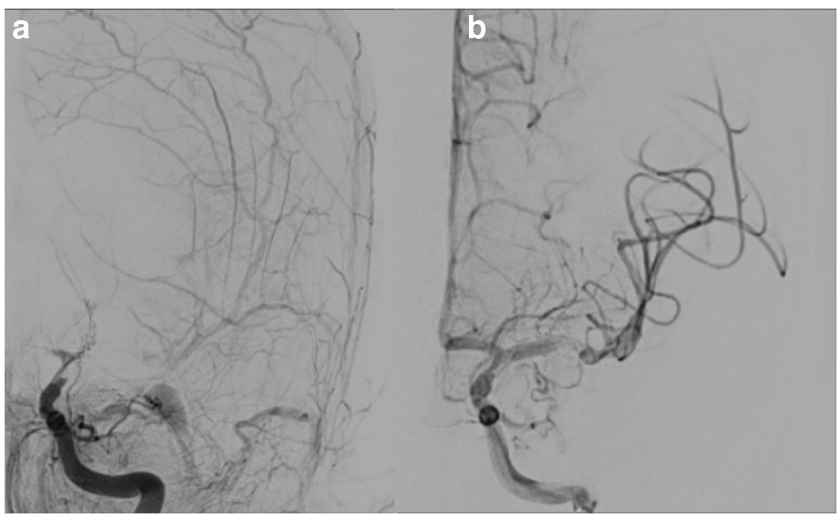

Fig. 2. Nine-year-old girl with a thrombus occluding the supraclinoid ICA. **a** Angiogram showing a thrombus occluding the left ICA bifurcation. **b** Final angiogram after thrombus aspiration. TICI 2B.

In adult patients, MT for AIS is a reliable therapy supported by reports of positive results (ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THERAPY, and THRACE). These studies showed the benefit of endovascular treatment in selected patients with acute large artery occlusion (LAO) after 6 h of symptoms onset [48].

A recent study proved that patients having a mismatch between clinical deficits and infarct size in MRI could undergo MT for up to 24 h after symptoms onset [49••].

Most of the information regarding MT procedures in children is obtained from case reports and review papers. In all of them, patients who underwent endovascular treatment for AIS in LAO had a good outcome even when the procedure was performed beyond 24 h of the beginning of the symptoms [50–55].

On the other hand, MT achieves complete recanalization with lesser complications than intraarterial therapy with fibrinolytics [2••].

One-third to 50% of children experienced good outcome without any endovascular therapy for AIS [2••].

Some special considerations must be taken into account when MT is considered to be performed in children:

1. The size of the femoral arteries in infants precludes the use of large catheters commonly used for MT.
2. The amount of contrast media and radiation exposure must be reduced to the minimum.
3. Most AIS are caused by arteriopathies. The diseased arterial wall could be damaged by the device used for the thrombectomy.
4. There is no solid evidence supporting endovascular treatment of AIS in children.

It can be concluded that MT in selected population is safe and technically feasible.

In the absence of a well-designed pediatric clinical trial, MT should only be considered in children with confirmed LAO and PedNIHSS ≥ 6.

Intraarterial fibrinolysis

In intraarterial fibrinolysis, a fibrinolytic drug is injected directly over the occluding thrombus in a cerebral artery through a microcatheter. Use of fibrinolytics in pediatric patients is controversial because the key components of the fibrynolitic system have quantitative and qualitative differences during childhood as compared with adulthood [56].

Intravenous thrombolytic therapy

Intravenous systemic thrombolytic therapy administered within the appropriate therapeutic time window after stroke onset has shown to improve outcome in adult AIS [57]. Currently, there is no evidence to support its use in children. Only small pediatric series or case reports have been published and must be analyzed with caution considering a probable bias due to underreport of complications. The Thrombolysis in Pediatric Stroke (TIPS) study was designed to assess safety, best dose, and feasibility of intravenous t-PA administered within 4.5 h of AIS onset. The study was stopped due to low patient recruitment.

However, it helped to analyze the diagnostic process of hyperacute AIS in children highlighting that delay in its recognition was a main obstacle to an early intervention [28••, 38•, 58].

Neurosurgical treatment

Increase of intracranial pressure (ICP) in the course of AIS is a life-threatening situation. According to the experience obtained from adult patients, early neurosurgical intervention may be necessary in order to perform a decompressive hemicraniectomy in cases of malignant MMCAI infarction in children [2••, 33••]. Besides, in cases of cerebellar infarction, a ventriculostomy may be necessary for developing hydrocephalia. Posterior fossa decompression in the cerebellar edema should be carried out as a prevention of cerebellar herniation and brainstem compression [2••, 38•].

ICP monitoring in adults with malignant infarctions has not been proven beneficial and may delay decompressive surgical treatment [59].

A recent study in a large sample of adult patients showed a strong association between late decompressive surgery and poor outcome [60].

Performing decompression before herniation may be the most important temporal consideration, even more in children, in whom cerebral atrophy is not present and though does not help to tolerate swelling.

Decompression treatment in children with malignant edema of the cerebral hemisphere may be effective and potentially life-saving. Understanding of the subsequent neurological state by the patient's family should be taken into account in decision making.

In children with large-volume infarctions, the medical team should consider performing early prophylactic hemicraniectomy within the first 24 h of the stroke onset, or implement a clinical and neuroimaging follow-up within the first 72 h for swelling monitoring and the eventual need for urgent surgery [2••].

Smith et al. reported ten children with ischemic stroke due to MMCAI and moderately good neurological outcome after decompressive craniectomy regardless of the stroke etiology, minimal GCS, involvement of multiple vascular territories, or the dominant hemisphere compromise. As mentioned, ICP monitoring may delay surgical treatment without benefit in the initial management of MMCAI [36••, 61].

Primary stroke prevention

AIS primary prevention in childhood is difficult to achieve since risk factors are mostly not predictable. Two exceptions are SCD and acquired or CHD.

Children with SCD have increased risk of AIS. Transcranial Doppler ultrasonography (TCD) identifies high-risk patients. Two randomized control trials, STOP and TWiTCH, have shown a significant reduction in the risk of first stroke in patients with abnormal TCD who undergo long-term regular red blood cell transfusions or receive hydroxyurea therapy after 12 months of regular red blood cell transfusions [62, 63]. Children with SCD who develop moyamoya syndrome may undergo surgery for cerebral revascularization [2••].

Efficacy of primary prevention with antithrombotic therapy in adults with mechanical heart valves has been clearly demonstrated and its recommendations are extrapolated to children with this condition. Stroke after Fontan

surgery occurs in 1–19% of children and either antiplatelet therapy or anticoagulation is recommended for primary thrombosis prevention. In case of dilated cardiomyopathy and myocarditis primary prophylaxis with antithrombotic therapy is still under debate. Incidence of stroke and pulmonary embolism while awaiting cardiac transplant is 2–6% and 30%, respectively. There is a grade 2C recommendation in favor of anticoagulation at least since the patient activation on a cardiac transplant waiting list [2••, 64].

Secondary stroke prevention

To date, there are no randomized control trials providing clear evidence of the optimal antithrombotic therapy in children with AIS. Treatment is aimed at reducing thrombus progression during acute stroke followed by long-term secondary prevention after the first ischemic event. Currently, many treatment decisions are extrapolated from evidence-based practice in adults. However, there are well-documented age-dependent differences in the hemostatic system, so indications, doses, and pharmacokinetics of antithrombotic drugs must be adjusted for each age group [2••, 33••, 64].

Reported recurrence rates for AIS or TIA were 10 to 50% when patients did not receive antithrombotic therapy [65•, 66, 67]. Arteriopathies, cardioembolic strokes, and prothrombotic disorders have the highest recurrence risk, especially in the first months after AIS onset [2••, 68, 69].

In AIS related to an embolic source or to prothrombotic disorders, most pediatric stroke guidelines recommend anticoagulant therapy. On the contrary, in AIS related to in situ thrombosis or arteriopathy, antiplatelet therapy with aspirin may be the first choice. For intracranial dissection given the potential risk of subarachnoid hemorrhage, aspirin may be preferred. For children with stroke of uncertain origin, it is not clear which antithrombotic therapy is better to start while investigating associated risk factors. Both the AHA and ACCP guidelines suggest either anticoagulation or antiplatelet therapy until the origin of AIS is determined. By contrast, UK guidelines suggest initiating treatment with aspirin based on its both low cost and low risk of bleeding [2••, 67, 68, 70].

Currently, there is sufficient evidence to establish the safety of both anticoagulant and antiplatelet therapies; only one report referred a 4% intracranial hemorrhage in an anticoagulation cohort [66, 71, 73].

However, there is scarce evidence to guide the timing of antithrombotic therapy initiation. Based on expert opinion, waiting 1–2 weeks before starting therapy in moderate-sized and large infarcts would be reasonably safe, effective, and could reduce the risk of major hemorrhage. In some cases, the risk of recurrent stroke might outweigh the risk of intracranial hemorrhage, so anticoagulation might be promptly required. In these circumstances, it is recommended to perform cranial imaging regularly [71–74].

The antiplatelet therapy most frequently used is aspirin dosed at 1–5 mg/kg/day. In case that aspirin use is contraindicated, clopidogrel might be a suitable option [74]. Anticoagulant drugs used in childhood include unfractionated heparin, low molecular weight heparin, and vitamin K antagonists and must follow pediatric recommendations for doses and laboratory monitoring [64].

Children guidelines recommend secondary stroke prevention treatment for 2 to 5 years. However, if risk factors preclude recurrence (e.g., continued cerebral

artery stenosis, persistent CHD, prothrombotic disorders), extended and even life-long antithrombotic therapy may be indicated [64, 70].

Conclusions

Unlike adult stroke where the rapid diagnosis allows adequate treatment, the diagnosis of stroke in pediatrics is often delayed due to low index of suspicion. Thus, increasing awareness of stroke is important. Implementation of evidence-based protocols and decision tools leads to rapid stroke diagnosis upon arrival to hospital. The development of a "stroke code" to be used by a multidisciplinary team should be a research priority in pediatric centers.

Tertiary pediatric centers with neuroimaging and neurointerventional expertise must carry out prospective studies to establish efficacy and safety of endovascular stroke management. Although safety of both anticoagulant and antiplatelet therapies had been established, randomized control trials providing evidence of the optimal antithrombotic therapy in children with AIS are needed.

Compliance with Ethical Standards

Conflict of Interest

Monica Ana R. Centeno declares that she has no conflict of interest. Maria Celeste Buompadre declares that she has no conflict of interest. Flavio Requejo declares that he has no conflict of interest. Carlos Rugilo declares that he has no conflict of interest. Carolina Cervio declares that she has no conflict of interest. Gabriela Sciuccati declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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