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Arterial ischemic stroke in non-neonate children: diagnostic and therapeutic specificities

M Kossorotoff[1,2], S Chabrier[1,3,4], K Tran Dong[1], S Nguyen The Tich[1,5], M Dinomais[1,6]

1. French Center for Pediatric Stroke, France
2. Pediatric Neurology, APHP University Hospital Necker-Enfants malades, INSERM U894, Paris, France
3. INSERM and Lyon University, U1059 Sainbiose, Saint-Étienne, France.
4. CHU Saint-Étienne, Service de médecine physique et de réadaptation pédiatrique, INSERM CIC1408, Saint-Étienne, France
5. Pediatric Neurology, CHU Lille, Lille, France
6. CHU Angers, Department of Physical and Rehabilitation Medicine, University of Angers, France.

Corresponding author

Dr Manoëlle Kossorotoff

Centre national de référence de l'AVC de l'enfant

Service de neuropédiatrie

Hôpital Universitaire Necker-Enfants maladies

149 rue de Sèvres

75015 Paris

France

Manoelle.kossorotoff@aphp.fr

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Abstract

Pediatric arterial ischemic stroke (AIS) is a severe condition, with long-lasting devastating consequences on motor and cognitive abilities, academic and social inclusion, and global life projects. Awareness about initial symptoms, implementation of pediatric stroke code protocols using MRI first and only and adapted management in the acute phase, individually tailored recanalization treatment strategies, and multidisciplinary rehabilitation programs with specific goal-centered actions are the key elements to improve pediatric AIS management and outcomes. The main cause of pediatric AIS is focal cerebral arteriopathy, a condition with unilateral focal stenosis and time-limited course requiring specific management. Sickle-cell disease and moyamoya angiopathy patients need adapted screening and therapeutics.

Keywords

Stroke, children, thrombolysis, stroke code, focal cerebral arteriopathy, rehabilitation

Abbreviations

AIS : arterial ischemic stroke, ASL : Arterial Spin Labelling, ASPECTS : Alberta Stroke Program Early CT Score, FAST scale : Face Arm Speech Time scale, FCA : focal cerebral arteriopathy, ICF : International Classification of Functioning, Disability and Health, ICU : intensive care unit, IPSS : International Pediatric Stroke Study, IV : intravenous, MDT : multidisciplinary team, MMA : moyamoya angiopathy, mRS : modified Rankin Scale, PedNIHSS : Pediatric NIH Stroke Scale, PSOM : Pediatric Stroke Outcome Measure, WISC : Wechsler Intelligence Scale for Children.

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Abstract

Pediatric arterial ischemic stroke (AIS) is a severe condition, with long-lasting devastating consequences on motor and cognitive abilities, academic and social inclusion, and global life projects. Awareness about initial symptoms, implementation of pediatric stroke code protocols using magnetic resonance imaging first and only and adapted management in the acute phase, individually tailored recanalization treatment strategies, and multidisciplinary rehabilitation programs with specific goal-centered actions are the key elements to improve pediatric AIS management and outcomes. The main cause of pediatric AIS is focal cerebral arteriopathy, a condition with unilateral focal stenosis and time-limited course requiring specific management. Sickle-cell disease and moyamoya angiopathy patients need adapted screening and therapeutics.

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pediatric stroke outcome measure, SCD: sickle-cell disease, WISC : Wechsler intelligence scale for children.

1.1. Definition, Epidemiology

Pediatric arterial ischemic stroke (AIS) in non-neonate children, by definition occurring in children aged 29 days to 18 years, represents about 1% of all strokes, with a reported incidence of 1-3 per 100,000 children per year in developed countries [1–6]. It is a severe condition, with a mortality rate of about 5%, which increases up to 15% in case of recurrence [7–10], and long-term consequences are frequent. At least two-thirds of survivors will suffer from often underestimated long-term sequels such as developmental (motor, global intellectual, language, etc.) and behavioral disabilities or epilepsy, leading to low adaptive and academic skills in day-to-day community, and less engagement, participation, and life-course perspectives [7–13]. As a consequence, it often leads to more stress, anxiety, and depression, in family's everyday life [14,15]. About 10% of people living with stroke consequences had their stroke during childhood, emphasizing these long-lasting and impairing consequences.

1.2. Diagnosis in the acute phase, pediatric stroke code protocols

1.2.1. Clinical presentation

Clinical presentation of AIS in children is rather similar to the adult presentation. But lack of awareness in the general public and physicians is the main point preventing an easy and rapid diagnosis. In most cases, AIS in children will present with acute, focal afebrile symptoms: hemiplegia and aphasia (which may be difficult to identify in toddlers). Posterior circulation stroke may in addition present with cerebellar symptoms and cranial nerve palsy. Seizures are frequent in the acute phase, especially in younger children and do not preclude the diagnosis.

The pediatric NIH stroke scale (PedNIHSS) evaluates the same 15 items as the adult scale, with similar minimum and maximum scores, many of its items being adapted to be developmentally appropriate [16]. The PedNIHSS has excellent interrater reliability and is the standard acute evaluation tool for both clinical purpose and research protocols in children with AIS. However, pediatricians are not familiar with it and it is not largely used yet in the pediatric setting except in research studies.

1.2.2. Imaging confirmation: MRI first and only

Despite difficulties in magnetic resonance imaging (MRI) availability the need for sedation in some children and a higher frequency of stroke mimics, early MRI is mandatory in children suspect of stroke. The feasibility of obtaining early MRI with rapid sequences, without sedation in the pediatric emergency department [17,18] has been demonstrated, [19].

Criteria for positive MRI diagnosis of AIS are similar to those for adults. Perfusion sequences without intravenous infusion, using arterial spin labeling (ASL) are of interest in children to search for a diffusion-perfusion mismatch. Furthermore, beyond diagnosing stroke and differentiating it from stroke mimics this “MRI first and only” attitude was demonstrated to improve the whole emergency neuropediatric and neurosurgical pathway [17].

1.2.3. Efficiency of pediatric stroke code protocols

In order to decrease time to imaging and for decision making, acute pediatric stroke protocols have been developed in several countries. This requires an *a priori* close collaboration between pediatric and adult neurologists, and neurointerventionalists. As stated by Bernard et al.[20],

“establishment of pediatric acute stroke centers with clinical and system preparedness for evaluation and care of children with acute stroke, including use of a standardized protocol for evaluation and treatment of acute arterial stroke in children that includes use of intravenous tissue-tPA” should result in increased preparedness, ability to offer these treatments to pediatric patients and increased safety. Two recent studies reporting the use of recanalization therapies in children from the Paris-Ile-de-France area (France) [21], and the Swiss neuropediatric stroke registry (Switzerland) [22] provided evidence for the benefits of regional stroke networks, which draw on the considerable expertise of adult stroke neurologists and neurointerventionalists. In the French study, acute protocols were implemented by a multidisciplinary working group that included pediatric neurologists, intensivists, emergency room pediatricians, vascular neurologists from the adult stroke unit, and diagnostic and interventional neuroradiologists. Regional health officers have also been included in the working groups. Equally important, pre-hospital emergency medical services providers were educated about pediatric stroke and trained in the use the face arm speech time (FAST) scale to consider stroke in children, and of the possible eligibility of children for acute recanalization treatment. Both advantages of such protocols were to ensure rapid recognition of AIS and make recanalization treatment eligibility possible.

1.3. Recanalization treatments: what is done and how to improve?

1.3.1. Recommendations

Current pediatric views on the use of acute thrombolytic therapy balance between an official non-thrombolysis recommendation unless being part of a clinical trial, and a more pragmatic attitude, arguing notably that if age is the sole contra-indication, thrombolysis should be

considered [23,24]. An individually tailored strategy seems justified: consider intravenous thrombolysis for children and adolescents who fulfill adult guidelines criteria, especially when one of these criteria is present: i) occlusion of a main arterial trunk, ii) major thrombophilia, iii) cardio- or artery-to-artery embolism, and iv) basilar occlusion with clinical and imaging signs of severity [24,25]. Intra-arterial thrombolysis or endovascular thrombectomy may be considered in selected patients fulfilling these criteria but with contra-indication for systemic thrombolysis (recent major surgery, interventional procedure, trauma, effective anticoagulant treatment, etc.) or delayed diagnosis: up to 8 hours from symptom onset in supra-tentorial stroke and up to 24 hours in case of basilar artery occlusion [25,26].

Recent recommendations highlighting the interest of thrombectomy in adults, alone or in a bridging strategy with intravenous thrombolysis followed by endovascular thrombectomy, led to many discussions about the pros and cons of thrombectomy in children. Experts' opinions [27] are in favor of thrombectomy in specific settings, such as thrombo-embolic AIS in patients over 5-10 years of age. In France, national authorities for the regulation of drug use (*Agence Nationale de Sécurité du Médicament*) recently extended the authorized age window for the use of intravenous r-tPA in the acute phase of stroke from the age of 16. The time window may also be extended considering the results of the recent adult DAWN and DEFUSE 3 studies which led to modifications in adult thrombectomy recommendations [28].

1.3.2. Limits for pediatric access to recanalization treatments

First of all, the main barrier to access eligibility for recanalization treatments is often the lack of recognition of pediatric stroke, leading to a long delay from symptom onset. As a consequence, childhood AIS is rarely diagnosed within the 4.5 hours window for consideration for intravenous tissue plasminogen activator (tPA) treatment and efforts are much needed on

this important issue [29]. Both pre- and post-hospital delays occur with a significant increase in time to diagnosis in outpatients versus inpatients for whom it is still nearly one day… Longer delay has also been associated with posterior circulation stroke, non-abrupt onset, milder or shorter duration symptoms, altered level of consciousness and presentation after working hours [30–33]. However, some children with large artery occlusion who are not diagnosed within 4.5 hours may theoretically still be eligible for thrombectomy.

Some technical issues have been raised for younger children, in whom smaller artery diameters may limit the use of endovascular devices, such as stent retriever devices employing balloon occlusion catheters, resulting in increased risk of distal embolism. From the age of 5 years old, artery diameters seem however large enough to support the use of classical endovascular thrombectomy devices [34]. Other considerations include radiation exposure and the toxic effects of iodine during angiography, which may limit the number of runs, the need for general anesthesia, and the higher risk of vasospasm in children.

Beside technical or organizational difficulties, the need for an individually tailored strategy established by multidisciplinary experts for a real-time decision making represents an additional difficulty

1.3.3. Reported experiences in children, ongoing and future studies

Reported experiences provide evidence favoring good safety of intravenous r-tPA, but safety of endovascular thrombectomy and efficacy of these treatments in children remain debatable.

1.3.3.1. Safety of r-tPA

In a retrospective analysis of 687 children longitudinally enrolled in a 15 year-period in the International Pediatric Stroke Study (IPSS) [35], 15 children received intravenous tPA. Symptomatic intracranial hemorrhage was observed in 26% of patients. Two children died from malignant infarct and only one of the 13 remaining survivors was neurologically normal at discharge. In this study, children had severe stroke and were treated off guidelines regarding time frame and severity. This may not reflect actual tPA safety in the recommended conditions of use. In the recently published French (12 children received intravenous r-tPA within 3 years) and Swiss (n=6) studies [21,22], thrombolysis was administered according to standard adult recommendations. No serious adverse treatment-related event was reported. These findings plead for sticking to standard adult inclusion and exclusion criteria in the pediatric protocols that should be written and shared between professionals in an upstream manner, and performing an individualized multidisciplinary decision in real time in order to provide better safety conditions.

1.3.3.2 Application of adult imaging tools to select candidate patients

The Alberta stroke program early CT score (ASPECTS) grades stroke findings on computed tomography (CT) and was used in several trials to assist in patient selection [36–38]. ASPECTS was modified for pediatric use on MRI (modASPECTS), first to predict future seizures after neonatal AIS and then to estimate infarct volume after childhood and neonatal stroke [39,40]. This pediatric tool may be implemented in clinical practice to assist with identification of patients who may be considered for endovascular treatment.

1.3.3.3 Indication of thrombectomy relative to stroke cause

The most difficult part in choosing recanalization treatments in pediatric AIS is to evaluate which children may benefit from treatment. Pragmatic indications are used by clinicians, relying on the supposed mechanism of stroke. In children, cardioembolism or artery-to-artery embolism is less common than intracranial arteriopathies. Although thrombotic or thrombo-embolic causes seem to represent a group of good indications for thrombectomy, altered vessel wall in arteriopathies is more subject to discussion as to whether it represents an increased risk of complication and/or treatment inefficiency [41]. Given the lack of safety and efficacy data, use of endovascular treatments is currently center-dependent and must be considered carefully on a case-by-case basis. When endovascular treatment in a patient younger than 18 years of age is considered, adherence to adult eligibility criteria is critical. This may also require informing the child in a way that meet his/her communication needs [42]. According to the country regulations, parents may sign a written general agreement for medical decisions concerning their child during inpatient stay and they should always be informed of medical decisions regarding their child.

1.3.3.4 Ongoing and future studies

The TIPSTERS study, using extended results from the TIPS study, will collect uniform data on all children who have received tPA at institutions that set up a pediatric stroke code protocol during the TIPS trial, either at the center or prior to transfer, as well as information on the use of acute endovascular therapies. Objectives are to establish preliminary safety data for intravenous tPA with the outcome measure of symptomatic intracranial hemorrhage or severe hemorrhage within 36 hours of tPA. The French nationwide Kid-Clot study is collecting data

on patients under 18 years of age who received intravenous tPA and/or endovascular thrombectomy in 2015-2018. Goals include assessment of the feasibility and success of pediatric stroke alert protocols, determination of intravenous tPA and endovascular therapy, and the delineation of criteria for additional pediatric guidelines concerning recanalization treatments

1.4. General management in the acute phase

1.4.1. Nonspecific general management in children

Children with acute AIS must be managed in a pediatric intensive care unit (ICU). For adolescents, hospitalization in a neurovascular ICU is also a possibility.

Recommendations concerning the general management in the acute phase were revised by the United Kingdom Royal College working group in 2017 [42]. The following management is recommended:

- Maintain general homeostasis, notably blood pressure, temperature, oxygen saturation and CO_2 blood concentration, fluid, glucose and electrolyte, heart and respiratory rates
- Use the PedNIHSS and age-appropriate Glasgow Coma Scale or AVPU 40 ('alert, voice, pain, unresponsive') to assess neurological status and consciousness level respectively.
- Withhold oral eating and drinking until swallowing safety has been established.
- Children should only receive blood pressure lowering treatment in the following circumstances: i) patients who are otherwise eligible for intravenous thrombolysis but in whom systolic blood pressure exceeds 95th percentile for age by more than 15%, ii)

hypertensive encephalopathy, iii) end organ damage or dysfunction, e.g. cardiac or renal failure.

- Preventive anticoagulation is only proposed for post-pubertal children.

Ensure that legal representatives have given consent for medical decisions according to the country regulations.

1.4.2. Secondary prevention treatments

Except for sickle-cell disease (SCD), there is a lack of controlled pharmacological studies in the field of childhood stroke. In our evidence-based age, there is thus no unequivocal answer on the best way to treat children with ischemic stroke due to cerebral stenosing arteriopathies. Nevertheless when comparing with historical controls or when looking to observational retrospective studies, there is a trend for a better outcome and few recurrences in children treated with antithrombotics (mainly with aspirin; anticoagulant having not showed a supplemental benefit) [43]. As half of recurrences occurs within 3 months and about all within 12 months after the initial event, and as stroke rarely recurs when the arteriopathy has stopped its progression, aspirin 3-5 mg/kg body-weight daily is recommended for at least 18 months to 2 years [23,42,44].

Indeed, the outcome depends primarily on the clinical course (progression vs stability/regression) of the arteriopathy, knowing that stroke rarely recurs when the stenosis has stopped its progression [4,43,45,46].

1.4.3. Specific management of sickle-cell disease patients

Cerebrovascular disease selectively affects children with the HbSS or HbS-β0 genotype. The incidence of stroke peaks between 2 and 5 years of age (1.02/100 patient-years) and increases with the severity of the anemia.

Primary stroke prevention:

- annual transcranial Doppler (TCD) screening from 2 to 16 years of age, to stratify stroke risk.
- If abnormal TCD (elevated blood-flow velocities, time averaged mean velocity >200 cm/s): start chronic transfusion program. The role for hydroxycarbamide in children with abnormal TCD findings is under investigation.

Acute stroke management:

- The sudden onset of a focal neurological abnormality in a patient with SCD suggests a stroke.
- MRI is recommended to confirm the diagnosis. Yet, because of the high risk of stroke in this population, when brain imaging cannot be performed quickly, probabilistic treatment should be started without delay.
- Acute treatment: emergency exchange transfusion with the following targets: HbS ≤30% and total Hb ≤12 g/dL. Exchange transfusion produces immediate hemodynamic and rheological effects [47,48]. To avoid hypotension or hypertension, automated procedures should be preferred [49]. In case of an expected procedure delay a simple transfusion is recommended to obtain a Hb level around 10 g/dL [48].
- To date, thrombolysis is not recommended because the nature of the intravascular obstacle in SCD is not pure fibrin clot.

Secondary stroke prevention:

- Chronic blood transfusion is mandatory unless hematopoietic stem cell transplantation can be performed [50].

1.4.4. Specific management of pediatric patients with moyamoya angiopathy

Ischemic presentation of moyamoya angiopathy (MMA) is the most common in children.

Stroke prevention and management of hemodynamic risk factors:

- Be aware of particular vulnerability to hemodynamic changes.
- Patient and physicians' education towards these risk factors, mainly vasoactive drugs, and general anesthesia [51].

Acute stroke management:

- Maintain homeostasis to avoid extension of ischemic lesions due to hemodynamic insufficiency. Targets are particularly tough in this setting.
- No recommendation can be made regarding intravenous thrombolysis and endovascular treatment in this setting, which has been classically considered in adults as at risk for secondary hemorrhage [52].

Surgical revascularization:

Indication of surgical revascularization should be discussed on a case-by-case basis using a multidisciplinary approach (with a dedicated meeting), at least involving neurologists, child neurologists, neurosurgeons and anesthesiologists.

Discussion will address:

- History of transient ischemic attack or cerebral infarct.
- Progression of angiopathy on imaging and related cerebral hypoperfusion
- Efficacy of collateral pathways,
- Functional status and age of the patient (more severe prognosis of MMA in infants [52].)

- A delay of a few weeks should be observed before the surgical revascularization in case of recent cerebral infarct.

1.5. Main causes and etiological work-up

1.5.1. The predominance of arteriopathic causes of AIS in children

Stenotic cerebral arteriopathy is identified as the AIS etiology in 60-80% of previously healthy children and the course of this arteriopathy is the strongest predictor of recurrent events. 30-40% of these children have a unilateral focal cerebral arteriopathy (FCA) characterized by a unique form of arterial insult with unilateral focal stenosis of the terminal carotid trifurcation and a characteristic monophasic course [43]. Childhood FCA is suspected to be an inflammatory vessel wall pathology triggered by infections, typically varicella. As recurrences occur for the great majority in the first 6 months after the index event, with further stabilization/regression of arterial stenosis and no further recurrence, aspirin 5 mg/kg/day is recommended for at least 18-24 months [53–59]. Stroke rarely recurs when the stenosis has stopped its progression [29,60,61]. Characteristics, pathophysiology, and research about FCA are further detailed in section 1.7.

Indeed, the outcome depends primarily on the clinical course (progression vs stability/regression) of the arteriopathy, and in a few cases arteriopathy may be chronic or progressive.

While primary angeitis of the central nervous system is rare in children, MMA and sickle-cell disease-related arteriopathy are the most frequent forms of chronic intracranial arteriopathy in children. Both typically develop on the carotid T, i.e. end of the internal carotid artery and proximal segments of its branches [43]. In SCD patients, intracranial arteriopathy mostly

appears before the age of 10 years thus screening starts as early as the age of two (see Section 1.4.3).

Some inflammatory processes described in FCA may be close to those described in vertebral artery dissection / arteriopathy. This is a quite specific pattern in which one or recurrent strokes occur in the posterior territories, and predominate in school-aged and adolescent males without identified trauma. The angiographic course of the disease is quite similar to FCA, once again with a monophasic course towards stability/regression/artery occlusion, without long-term recurrence. The preferred modality of stroke recurrence prevention is anticoagulation in this setting [62,63]. Carotid artery dissection is not frequent in young children.

1.5.2. Thrombo-embolic causes

Thrombo-embolic causes account for 20-30% of causes of pediatric AIS. Cardiac embolus is found mainly in malformative cardiac conditions with a right-to-left shunt (or equivalent) and in acquired hypocontractile diseases (myocarditis, myocardiopathy). Actually, thrombophilia responsible for arterial stroke is not frequently encountered. Autoimmune disease and nephrotic syndrome should be looked for as they represent the main causes of acquired thrombophilia in children (see section 1.5.3).

1.5.3. Proposed etiological work-up

Several recommendations have been published concerning etiological work-up in pediatric AIS [42]. The authors propose the following investigations:

- **Comprehensive clinical evaluation**: history of prior infection (especially VZV <12 months), recent immunization, dysmorphic features, neurocutaneous stigmata, autoimmune disease, and evidence of vascular disease in other organ systems
- **hematological investigations**, including full blood count. In case of anemia, check for iron status (e.g. iron, ferritin, total iron binding capacity) and hemoglobinopathy.
- **biochemistry tests**, including kidney and liver assessments, and fasting cholesterol.
- **thrombophilia testing**, including lupus anticoagulant and antiphospholipid antibodies (anticardiolipin and anti-β2GP1 antibodies), total plasma homocysteine
- **inflammation and infection tests**, including viral blood serology according to patient's history and cerebrospinal fluid assessment for inflammatory meningeal reaction in case of intracranial arteriopathy
- **cardio-vascular evaluation**: electrocardiogram, contrast-enhanced transthoracic echocardiogram to search for patent foramen ovale, cerebrovascular imaging from the aortic arch to vertex, with CT angiography or magnetic resonance angiogram, transcranial Doppler in patients with SCD

1.6. Stroke mimics in children

Actually, the majority of stroke alerts attended by pediatric stroke specialists ultimately are stroke mimics, including non-stroke neurological emergencies [17,64–66], leading to an MRI-first strategy in children [66]. Migraine is the most common stroke mimic in children [17,28,64,65]. Other diagnoses include seizure with Todd's paralysis, demyelinating disorders, conversion disorders, and central nervous system tumors [17,28,67,68].

1.7. The specificity of FCA: pathophysiology and insights for future studies

As mentioned in section 1.5.1, childhood FCA is a specific clinical and radiological pattern. It is suspected to be an inflammatory vessel wall pathology triggered by varicella (also named post varicella angiopathy, PVA) and other (viral) infections, with transient course (also called transient cerebral arteriopathy, TCA). Inflammation seems to play a crucial role in the pathogenesis of FCA: i) infectious agents, such as varicella and other common (viral) infections, act as major triggers for of this arteriopathy [54,57,59], ii) inflammatory changes in the vessel wall and parietal enhancement of affected vessels in MRI have been observed [69–72], and iii) some inflammatory biomarkers were associated with arteriopathy progression [58,73]. A recent score was published, allowing to assess radiological progression of FCA, correlated with recurrence and outcomes [74].

Because of the inflammatory process, using immunomodulatory drugs at the acute stage of FCA is the next step in further studies. Actually, immunotherapies, mainly steroids, are sometimes used by neuropediatricians for children with stenotic arteriopathies and AIS. Steroids have been largely used and managed by pediatricians for a long time in neuroinflammatory diseases of childhood and have been shown to be generally safe and reasonably well tolerated. European and Australian experts in the field of pediatric stroke expressed a consensus that a steroid trial in children with FCA was the most important and feasible childhood stroke treatment trial to set up [45,75–79].

In line with this, the pediatric arteriopathy steroid aspirin (PASTA) study is a European-Australian multicenter, parallel group, two-arm, randomized-controlled, open-label clinical trial blinded for outcome. The study primary objective is to determine if a short high dose course of methylprednisolone/prednisolone + standard of care would result in quicker recovery in children with AIS due to FCA versus standard of care alone. Secondary objectives are to study effects of

such management on i) clinical symptoms, i.e. functional clinical outcomes, rate of recurrence, epilepsy, long-term developmental sequels as well as their consequences in day-to-day life (notably academic issues), familial impact at 12 months, ii) angiographic pattern: residual stenotic arteriopathy, rate of evolution towards progressive arteriopathy, iii) with acceptable safety (frequency of infectious episodes, serious adverse effects), and iv) study effects in different age groups. PASTA study, expected to start in 2019, will be the first pharmacological randomized trial in children with AIS, except in the setting of SCD. A similar study is currently being built in the United States and joint efforts are made to homogenize criteria in order to be able to pool data to increase power.

1.8. Long-term follow-up: pediatric specificities

1.8.1. Outcomes

Stroke in children represents a different disease process from adults. Stroke during childhood interacts with brain maturation and developmental trajectory. The full impact of a stroke in a child may not be known for years until the child matures and reaches various developmental stages.

In terms of long-term outcomes, children and young people do not necessarily recover better than adults from stroke. This challenges the commonly held view that recovery is better in the child's brain than in the adult's [80]. However this view is a bit misleading and appears to be too simplistic. In fact, Mosch et al. [81] demonstrated that children and adults matched for infarct site (as well as possible) had similar levels of impairment.

There are few specific outcome measure assessment tools for pediatric stroke [82]. The pediatric stroke outcome measure (PSOM) is a standardized neurological exam/impairment level assessment tool, specifically validated in infants (≤2 years of age) and children and young

people (2-16 years) with arterial ischemic stroke. This tool is not available in a French version yet. A wide variety of measures for pediatric stroke outcomes have thus been used, including the Wechsler intelligence scale for children (WISC), the modified Rankin scale (mRS), etc.

Outcomes are highly variable in regards to the field of outcomes tested and etiology of stroke [42,83]. The spectrum of difficulties that patients experience after stroke in childhood is broad [84], with reported deficits in all domains of the International Classification of Functioning, Disability and Health (ICF) framework [85]. Data from the International Pediatric Stroke Study including more than 600 children with arterial ischemic stroke reported residual impairments in 74% of them [86]. Most studies estimate that over 50% to 70% of pediatric stroke patients will have long-lasting or persistent neurological deficits or develop subsequent cognitive, learning, seizure disorders, or developmental problems. Children may experience somatosensory impairments. Motor deficits, with a reported incidence between 50 to 80% [76,87,88], may include muscle weakness, altered muscle tone, loss of dexterity, and coordination of movement deficits may not be exclusively unilateral. After unilateral arterial ischemic stroke, nearly 100% of children will recover the capacity to walk. However upper limb function tends to be more severely affected and to recover less, as showed in adults. A wide spectrum of speech, language and communication impairments may be observed, with sometimes subtle difficulties in younger patients. Even if some children seem to function with an apparently 'normal' range of language, qualitative deficit may be found in in-depth language assessment. All of these impact activities, daily life, school functioning, and participation, with consequences on adult outcomes [12,84,87,89–92].

Factors which determine long-term outcomes are incompletely understood. Recognized prognostic factors, involved at various degrees, include [76,78] lesion characteristics (type, size, and location of stroke), the age at stroke onset and the age at which assessment is performed, developmental level and cognitive abilities before AIS occurrence, laterality of lesions, co-

morbidities, the child's environment (family functioning, social determinants) and access to resources, and the presence of seizures. A low PedNIHSS at the acute phase is the best predictor of having no symptoms or mild symptoms at 3-6 months [79]. Diffusion-weighted MRI signal abnormality along the cortico-spinal tract remote from stroke site is a predictive factor for subsequent motor impairment [93]. The persistence of language impairment 6 months after stroke is highly predictive of long-term language difficulties.

Effect of age at onset in predicting long-term outcome is variable. Children aged three years old or less at onset had poorer outcomes across all domains [94]. On the contrary, a focal insult occurring at an age of five years or less was associated with better outcomes regarding language performance [95]. This particular preservation of language even after lesions in the left middle cerebral artery territory may reflect brain plasticity of a still incompletely settled function, with the possibility to "transfer" function to the contralateral hemisphere. Nevertheless detailed cognitive assessments showed that children with right hemisphere supporting language had impairments in other cognitive domains, namely visuospatial function or overall IQ. Finally, Chen et al. [96] showed that children improved more in self-care and cognition if they were older than seven years of age, and had lower measures in each specific area at admission.

This emphasizes that children who suffered from a stroke may 'grow into their disability'. Hence, in the developing brain affected by a stroke, some impairment and deficits only become evident over time, such as disorders of higher brain systems, including memory, attention and executive functions, language difficulties or remote seizures encountered in later school years.

In consequence, patients who had a stroke in childhood require long-term follow-up and monitoring throughout their entire maturation and development. This must lead to ensuring optimal achievement at adulthood period of psychosocial (well-being), developmental, and functional status.

1.8.2. Rehabilitation programs

Although is difficult to provide clear recommendations regarding the timing, the nature, and the intensity of optimal rehabilitation approaches after stroke in childhood due to lack of strong evidence [77], most rehabilitation programs rely on key-points, some of which are highly specific to childhood:

- They involve a **multidisciplinary team** (MDT), including medical personnel, nursing, physiotherapy, occupational therapy, speech and language therapy, dietetics, clinical neuropsychology/clinical psychology, social work, orthoptics, play therapy. Individual therapies should complement each other to maximize functional skill re-acquisition.
- It is emphasized that MDT assessment and intervention should occur **early.** From the available literature there is growing evidence to suggest that early therapy improves the rate of recovery and improves outcome within the first six months after stroke[96].
- **Patient-centered individualized care plan** should be set up, considering the child and family priorities/preferences as well as age and developmental stage. The child and his/her family should be central to decision making, goal-setting, and individualized care.
- **Regular re-assessment of the patient's needs and care plan**: Identifying and assessing the rehabilitation needs of the child/young person relies on the understanding that these needs are likely to change over time (particularly at transition points, e.g. from primary to secondary education, from childhood to adulthood). The MDT approach should provide a rehabilitation program that fits within a neurological and developmental trajectory.

- **Motor rehabilitation** should focus on **specific goal-directed tasks** relying on principles of motor learning, which follow a distributed model of training with variation in type and duration of tasks to achieve specifics goals that have been set with the child/young people and their family and are meaningful and relevant to them. They use the SMART criteria, i.e. specific, measurable, agreed, realistic and time-bound goals/principles [94] and require sufficient intensity and repetition [97] *and for as long as they are willing and capable of participating and showing measurable benefit from treatment"*.
- **Cognition and speech therapies** should also involve parents/caregivers/educational team (school) in order to deliver optimal interventions to support speech, language, communication and cognitive functioning in the child's daily life activities and education. "*Teaching staff and allied health professionals should teach metacognitive skills, methods encouraging the ability of the child/young person to problem solve within the home, school and community.*"[97]
- **Prevention of secondary complications** is also crucial and requires multidisciplinary assessment and intervention. For example, attention to related complications of spasticity and orthopedic complications (limitation of active and passive range of motion, contractures, and scoliosis) by experts in physical medicine and rehabilitation is essential. Casting and posture are recommended as well as targeted injection of botulinum toxin into localized hypertonic muscles if necessary after two years of age [98].

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