Paediatric stroke — a review of current guidelines for diagnosis and treatment

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ABSTRACT

Stroke, increasingly recognised in children in recent years, is an important cause of long-term morbidity and disability. It can be classified by the stroke type as either arterial ischaemic stroke (AIS), haemorrhagic stroke (HS), or cerebral sinovenous thrombosis (CSVT). Furthermore, perinatal and childhood stroke can be distinguished. A wide range of conditions associated with paediatric stroke has been identified, which differ significantly from those in adults. A paediatric stroke can also present with a variety of symptoms and signs, both specific and non-specific. Because of the diversity of the underlying risk factors, limited awareness among the medical community, and therefore insufficient recognition of paediatric stroke symptoms, diagnosis can be difficult and is often delayed. This limits access to acute interventions. The goal of this paper was to examine the current guidelines for the diagnosis and treatment of paediatric stroke.

Key words: arterial ischaemic stroke, paediatric stroke, management, guidelines

Introduction

The World Health Organisation defines stroke as "a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin".

Stroke is an important cause of long-term morbidity and disability in children. It has been increasingly recognised in children in recent years. The overall incidence ranges from 2.1 to 7.8 per 100,000 per year [1–3]. For childhood arterial ischaemic stroke (AIS), the incidence is 1.60 per 100,000 per year, and among these the highest incidence occurs in those aged under one year, where the incidence is as high as 4.14 per 100,000 per year [4]. The estimated incidence is 1.2 per 100,000 per year for haemorrhagic stroke (HS) [5], and 0.25-0.67 per 100,000 per year for cerebral sinus venous thrombosis (CSVT) [6–9]. Stroke is among the top 10 causes of death of children in the United States, with an estimated mortality rate of around 5% [10, 11].

It is suggested that Asian and black children are at significantly higher risk of AIS than white children [4, 5, 12], while boys are at a higher risk than girls [5, 13].

Perinatal, neonatal and childhood stroke can be distinguished. The term ‘perinatal stroke’ describes a stroke that occurs between 28 weeks gestation and 28 days after birth, whereas ‘neonatal stroke’ concerns only the period of the 28 days after birth, while a ‘childhood stroke’ occurs between the ages of 29 days and 18 years. According to pathophysiological changes, two stroke types can be distinguished: HS and ischaemic stroke (IS) with its two subtypes CSVT and AIS [14].

According to a retrospective study based on the California state database from 1991 to 2000, 51% of cases of paediatric stroke were IS, whereas 49% were HS [5]. In children, as in adults, the most common type is AIS, accounting for 80% of neonatal strokes [15] and approximately 55% of childhood strokes [5, 16]. Around 15.4% of cases of paediatric AIS are bilateral and involve anterior circulation in around 80% of cases [17]. The rarest is CSVT, although in one study it was diagnosed in up to 25% of IS cases [18]. Those most frequently affected by CSVT are neonates [7].
Risk factors

A wide range of conditions associated with paediatric stroke has been identified (Tab. 1). These factors differ significantly from those in adults [19–22]. In a large-scale study by Mackay et al., the most common were arteriopathies (53%), cardiac disorders (31%), and infections (24%) [23]. In a study by Mallick et al., at least one risk factor for childhood AIS was identified in around 80% of cases and a significant number of children had multiple risk factors. Aetiology remained undetermined in around 10% of children [4]. In order to improve strategies for stroke prevention and reduce the risk of recurrence, it is essential to identify all the underlying risk factors.

Because of the diversity of these underlying risk factors, limited awareness among the medical community and therefore insufficient recognition of paediatric stroke symptoms, diagnosis can be difficult and is often delayed. Reported intervals have ranged from 16 to 25 hours from the onset of symptoms to the stroke diagnosis [24–26].

Clinical presentation

A paediatric stroke can present with a variety of symptoms and signs, both specific and non-specific. The clinical presentation depends on the type of stroke, the age of the child, and which vessels are involved. Stroke presentation in children and adolescents is notably distinct from that seen in adults. A non-specific character of manifestations of stroke is more frequent in younger children, whereas with increasing age the signs and symptoms are more similar to those of an adult.

In AIS, the most common symptoms are focal neurological signs, including hemiparesis, speech disturbance and visual disturbance. Non-focal signs are presented in more than half of children with AIS, including reduced level of consciousness, headache, seizures and papillodema [4, 23, 27, 28]. In the Canadian Paediatric Ischaemic Stroke Registry of 160 children with CVST, 76% of the children had diffuse neurological signs (including decreased level of consciousness, headaches, papillodema and jittery movements), 58% had seizures, and 42% had focal neurological signs [7]. Similarly to IS, the most common symptoms in HS are focal deficits, but non-focal signs are significantly more frequent than in AIS.

Depending on the age of the child, the presenting symptoms of stroke differ. Neonatal stroke mostly presents with seizures and non-focal neurological signs. Frequently abnormal tone and altered level of consciousness are observed. During the first days, neonates may also present feeding difficulty, increased crying, and lethargy. Irritability and sepsis-like symptoms with cold extremities have also been observed. Localised symptoms are infrequent in neonates, but among them the most frequent is lateralising hemiparesis. In comparison, older children have commonly focal neurological deficits in addition to non-specific symptoms [29–31].

Children may also present symptoms lasting < 24 hours, compatible with transient ischaemic attack (TIA). However, TIA among children is not well described and presumably underdiagnosed. In a US study investigating the prevalence of TIA in children in a large national database, the ratio of TIA requiring hospitalisation to stroke admissions was 1:4.8 [32].

Evaluation of clinical status

A proper assessment of a child’s clinical status is essential to provide the highest opportunity for survival. The most popular scale for paediatric stroke patients is the Paediatric

Table 1. Risk factors for childhood AIS and HS [4, 24]

<table>
<thead>
<tr>
<th>Risk factors for childhood AIS</th>
<th>Risk factors for childhood HS</th>
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<tr>
<td><strong>Arteriopathies:</strong> focal cerebral arteriopathy, moyamoya, arterial dissection, central nervous system vasculitis</td>
<td><strong>Vascular disorders:</strong> arteriovenous malformation, cavernous malformation, cerebral arterial aneurysm, moyamoya</td>
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<tr>
<td><strong>Cardiac disease:</strong> congenital cardiac disease, acquired heart disease, isolated PFO, post cardiac surgery (within 72 h), previous cardiac surgery or catheterisation, arrhythmia, atrial septal defect, ventricular septal defect</td>
<td><strong>Clotting disorders:</strong> severe platelet disorder, low platelet count, severe inherited bleeding disorder, anticoagulation, severe vitamin K deficiency</td>
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<tr>
<td>Sickle Cell Disease</td>
<td>Sickle Cell Disease</td>
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<tr>
<td><strong>Infection:</strong> varicella zoster, upper respiratory tract infection, multiple infections</td>
<td><strong>Illicit drug use:</strong> amphetamines, cocaine</td>
</tr>
<tr>
<td><strong>Genetic and acquired thrombophilia:</strong> factor V Leiden, PT20210, MTHFR c^77T, protein C deficiency, increased lipoprotein (a), high homocystinuria, antiphospholipid syndrome</td>
<td><strong>Other:</strong> cervical rib, iron deficiency anaemia, radiotherapy, high alpha 1 antitrypsin, head or neck trauma, under-vaccination, haematological malignancy, trisomy 21</td>
</tr>
<tr>
<td><strong>Acute systemic conditions:</strong> shock, dehydration, acidosis, hypoxia, fever for &gt; 48 hours, sepsis</td>
<td><strong>Chronic head and neck disorders:</strong> migraine, intracranial malignancy, cerebral aneurysm, ventricular shunt, PHACES syndrome</td>
</tr>
<tr>
<td><strong>Risk factors for childhood HS</strong></td>
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National Institute of Health Stroke Scale (PedNIHSS). PedNIHSS was developed by adapting all the exam items and scoring ranges of the NIH Stroke Scale (NIHSS) to an age-appropriate format. PedNIHSS is applicable especially for children over the age of two years. The scale is less accurately adjusted for children of two and under due to their limited language ability and the nonfocal character of symptoms [33].

In order to measure neurological recovery after stroke, the Paediatric Stroke Outcome Measure was developed. This scale is suitable for everyone from neonates to adults, and can be applied during the treatment of children as they recover [34].

**Differential diagnosis**

Childhood stroke can be mistaken for many conditions. Acute neurology symptoms are commonly qualified as presentations of more common alternative illnesses. Among 342 admissions of acute paediatric diseases affecting the brain, migraine (28%), seizures (15%), Bell’s palsy (10%), IS or HS (7%), and conversion disorders (6%) represented the five most common diagnoses [35]. Although listed in fourth place, stroke is not commonly considered by clinicians. This oversight leads to significant delays in diagnosis, and therefore decreases the chances for clinical trials of acute interventions [36, 37].

There are no specific symptoms of paediatric stroke. However, clinicians’ alertness in relation to a higher possible association with stroke should be raised when the patient presents with an inability to walk, facial and arm weakness, and where the patient had an unimpaired health status in the week preceding the first symptoms [38].

**Diagnostics**

Children presenting symptoms suggesting a higher risk of stroke should undergo an immediate neurological assessment including urgent neuroimaging [14].

Non-contrast head computed tomography (CT) is commonly used as the first imaging investigation in a child presenting with possible stroke, and this can rule out intracranial haemorrhage. Nevertheless, for the detection of AIS and conditions presenting similar clinical features, CT has limited sensitivity [39]. CT frequently shows no abnormalities within the first six hours in AIS [40, 41]. Outcomes of studies conducted in adults show there may be no significant changes in CT imaging up to 24h from symptoms onset. Therefore, using only CT can lead to diagnostic delays and impede access to reperfusion therapies.

Magnetic resonance imaging (MRI), especially diffusion-weighted sequence (DWI), is the most sensitive modality for the diagnosis of IS and is indicated as the most appropriate imaging investigation when IS is suspected. Nevertheless, compared to CT, apart from the limited availability and expensiveness, there is the problematic matter of MRI duration. Additionally, in children, MRI more frequently requires sedation or general anaesthesia. As a replacement for MRI in diagnosing IS, computed tomography angiography (CTA) has been proposed. A swift diagnosis is vital to enable the possible use of thrombolytic and endovascular interventions. Due to the prolonged duration of MRI, special rapid protocols have been developed [14, 42].

Australian guidelines recommend rapid MRI as the diagnostic imaging modality of choice when paediatric AIS is suspected. Where urgent MRI is impossible, CT imaging including CTA and CT perfusion can be considered as an alternative, particularly in older teenagers. When HS is suspected, CT and MRI are both acceptable and one or the other ought to be performed. It is also recommended to keep to a minimum the level of radiation exposure during head CT [14].

The Royal College of Paediatrics and Child Health (RCPC) guidelines recommend using MRI imaging only if it is available within one hour of admission to hospital. It is recommended to perform a CT scan within one hour of admission to hospital in every child with a suspected stroke. This should include CTA limited to intracranial vascular imaging if HS is demonstrated, or CTA (covering aortic arch to vertex) if the scan does not show a haemorrhage. Additionally, it is recommended to provide MRI if the initial CT is negative, and yet a stroke is still suspected [27].

To speed up the diagnostic process, it is vital to develop a diagnostic algorithm as presented in Figure 1 [14, 27, 43]. Proper diagnostics are built upon understanding the entire medical history and rapid sequence MRI where this is possible. In a case where urgent MRI is unavailable, low radiation CT is proposed. The exclusion of HS and the confirmation of AIS within 4.5 hours enable the consideration of intravenous administration of tissue plasminogen activator (t-PA) or thrombectomy.

In order to facilitate the accessibility of hyperacute reperfusion therapies and to shorten MRI time to 15-20 minutes, many centres have developed a hyperacute imaging protocol including: DWI and apparent diffusion coefficient (ADC) maps (confirming the diagnosis of a stroke) and susceptibility-weighted imaging (SWI) or gradient echo (GRE) to detect a haemorrhage [39]. A full diagnostic imaging protocol and diagnostic investigations are often required during the initial hospitalisation, even if the stroke is confirmed by the hyperacute protocol. Finding the initial cause contributes greatly to preventing recurrences.

**Treatment**

As stressed previously, clinicians still face multiple difficulties concerning diagnostics, clinical assessment and defining aetiology of a stroke in a paediatric patient. Due to the long delays preceding a conclusive diagnosis, the high frequency of stroke-resembling conditions, and the scarcity of stroke care teams and units within paediatric centres, it is very difficult to evaluate the advantages and risks of some types of acute treatment, e.g. thrombolysis.
The diversity of the underlying risk factors makes it challenging to correctly assess the primary cause of the stroke and administer causal treatment, if available. Furthermore, the age of the patient must be taken into account when making a decision about treatment. There are significant differences in managing a stroke in neonates, children and adolescents. It is also a matter of concern that the simple adoption of methods used in adults seems inappropriate, despite all the promising results and the evidence of benefit over risk. Differences between these two populations can most clearly be seen in terms of pathophysiology, aetiology, and developmental differences in the fibrinolytic system [such as lower endogenous plasminogen levels and higher plasminogen activator inhibitor-1 (PAI-1) levels].

The number of randomised or large studies is limited; therefore, the guidelines are based on expert consensus, smaller study reviews, cohort studies, and case report reviews. It is difficult to conduct a prospective study in a paediatric population, like TIPSS (Thrombolysis in Paediatric Stroke Study), which was closed because of the lack of patients that would hit the time window for t-PA. Guidelines differ slightly throughout the world, starting with the procedure after admission. Most experts agree about monitoring certain parameters in children with a suspected or confirmed stroke. While the diagnostic process is still in progress, it is recommended to maintain within normal limits selected medical parameters, which we will refer to as a 'hyperacute treatment' (Tab. 2). The aim of hyperacute treatment is to prevent further damage to the brain tissue.

Figure 1. Proposed diagnostic pathway in children with suspected AIS. Adapted from the Australian Childhood Stroke Advisory Committee’s Guidelines for the Diagnosis and Acute Management of Childhood Stroke 2017 and Rivkin MJ, Bernard TJ, Dowling MM, Amlie-Lef
Multiple ways of managing stroke are available. The patient's age, general and neurological condition, co-morbidities, and suspected aetiology of a stroke must be taken into account before making any decision concerning further treatment.

**Antithrombotic or anticoagulant therapy**

As the initial treatment of IS begins, antithrombotic or anticoagulant therapy such as aspirin (ASA), low-molecular-weight-heparin (LMWH), or unfractionated heparin (UFH) is recommended [44].

There have been no randomised controlled trials investigating the efficacy of these therapies in children, although most guidelines suggest it is reasonable to assume their safety based on the limited data available, and also that they prevent further ischaemic damage.

As contraindications of therapy, exclusion of dissection and embolic causes, and the presence of intracranial haemorrhage are indicated. It is strongly recommended that antiplatelets and anticoagulants shall not be administered within 24 hours after the neurovascular intervention. Additionally, there is no comparative data of high quality between antithrombotic and anticoagulant therapy in paediatric stroke. While ASA is believed to be safer and cheaper, it has been suggested that there will be better clinical outcomes when using heparins in the adult population. However, more studies need to be conducted to determine the best treatment schemes [13, 14, 27, 45, 46].

The RCPCH guidelines recommend the start of antithrombotic treatment at the presentation of AIS, in the absence of contraindications. Although there is not enough evidence to confirm which group of antithrombotic drugs (antiplatelets (ASA and clopidogrel) or anticoagulants (UFH, LMWH)) is better, the RCPCH guidelines recommend using 5mg/kg of ASA up to a maximum of 300mg within 24 hours of the diagnosis of AIS and, after 14 days, reducing to a dose of ASA 1mg/kg to a max of 75mg. Nonetheless, it is not recommended to be routinely given to children and young people with sickle cell disease (SCD). ASA is recommended because of its lower cost, less need for monitoring, and extensive clinical experience of its safety and tolerability.

Australian guidelines do not indicate a specific dosage of ASA. The recommendation of using antithrombotic drugs is weaker, although anticoagulation and antiplatelet therapies are considered to be safe in children with AIS after the exclusion of a haemorrhage.

**Thrombolytic therapy / revascularisation therapy**

After revolutionary outcomes of the trials of thrombolytic therapies in adults, there is a tendency to find criteria for safe administration of TPA to treat children with AIS. Randomised trials among adults have shown reduced disability and mortality; however, no such trial has been completed in children.
As mentioned before, there cannot be a simple extrapolation of protocols from adult to paediatric populations, due to factors including differences in pathophysiology and drug distribution. An attempt to find the safe maximal doses of intravenous t-PA in AIS was made in TIPSS [47], among three doses (0.75, 0.9 and 1.0 mg/kg), but the trial was closed due to a lack of patient recruitment. Most patients were beyond the time window to administer intravenous tPA (> 4.5h from the onset of stroke symptoms) [14, 43].

Despite the fact that most guidelines provided by associations from multiple countries do not recommend t-PA therapies outside clinical trials, a growing number of publications have described the use of this therapy in individual cases [14, 27, 48].

The Department of Neurology of the Boston Children's Hospital in the USA suggests using a dose of 0.9mg/kg of intravenous t-PA, which is similar to the dose used in the adult population. As mentioned before, there has been no study completed in children to optimise the t-PA dosage. Other studies have cited a range from 0.2 to 1.2mg/kg.

According to the RCPCH guidelines, the off-label use of t-PA may be considered in children with AIS aged over two while meeting special criteria (among them: confirmed AIS, acute neurological deficit, PedNIHSS score of 4-24 inclusive, remaining within the therapeutic window of 4.5 hours, the exclusion of intracranial haemorrhage, and a lack of contraindications). According to the Australian guidelines there are weak recommendations for using t-PA therapy. t-PA may be appropriate in specific children who fulfill special criteria similar to those defined by the RCPCH guidelines. Treatment with t-PA should only be considered in medical centres of high reference with an experienced team of neurosurgeons and neurologists. Decisions about the treatment should be made taking into consideration all precautions.

### Endovascular therapy

Another path being considered is endovascular therapy (EVT). In adults there have been favourable outcomes from six randomised controlled trials of endovascular thrombectomies in AIS. When comparing t-PA to EVT safety, the outcomes between these two groups are similar. Regarding clinical outcomes, in all studies patients have shown improved functional effects. Mainly it is the patients treated within six hours who achieve the best outcomes [49]. Despite the fact that no such trials have been conducted in children, there are an increasing number of successful individual cases of children with AIS who have received EVT [48, 50, 51]. Guidelines suggest considering EVT with stent retriever, with or without prior iv thrombolysis, especially among patients when: PedNIHSS score is more than 6, a favourable profile of salvageable brain tissue imaging has been proven, and the time from onset is 6-12 hours (according to different guidelines) [13, 14, 27].

### Decompressive craniectomy

Paediatric stroke can be associated with cerebral oedema. Clinicians should always be alert to increased intracranial pressure during the first 48 hours. The patient’s state should be carefully monitored, and if it worsens, access to an intensive care unit should be available. When cerebral oedema is suspected, it is recommended to elevate the patient’s head from 15 to 30 degrees while maintaining a midline position. During treatment of cerebral oedema, all precautions should be taken, therefore it is recommended to consult with more experienced clinicians before making a decision about hyperosmolar therapy or therapeutic hyperventilation. Proper management of the increased intracranial pressure may be life-saving.

Literature concerning decompressive craniectomy in children contains only retrospective reviews with no randomised control groups, although craniectomy is regarded as a life-saving treatment by some associations, e.g. the American Heart Society. Especially trials in adults with malignant infarction of the middle cerebral artery (MCA) have shown increased survival and improved functional outcomes. Infarction of a large territory can cause a life-threatening cerebral swelling, an increased intracranial pressure, and hence further ischaemia [13, 14, 27, 46, 52].

Decompressive craniectomy in MCA infarction is to be considered in children and young people under such circumstances as extensive MCA syndrome, MCA AIS with evidence of oedema/mass effect, infarction size > 50% of MCA territory or DWI volume of > 145 ml, worsening of/in PedNIHSS or GCS score. Treatment can be initiated within ≤ 48h from the onset of symptoms [14, 27].

### Rehabilitation

Early rehabilitation is crucial to optimise the outcome after childhood AIS. It should begin immediately, during the acute phase of the stroke. All children after a stroke should be initially assessed to determine the severity of the stroke and their rehabilitation needs [6]. Standardised assessment tools are recommended in the evaluation of impairments, e.g. The Paediatric Stroke Outcome Measure (PSOM) or the World Health Organisation’s International Classification of Functioning (ICF) [53].

### Outcomes and recurrence

Stroke significantly contributes to children’s mortality and morbidity. According to the data from the Global and Regional Burden of Stroke 2013, the mortality rate in 2013 was estimated to be 1.3 per 100,000 in the age group of 0–19 years. Globally, there were 29,026 deaths from HS and 4,043 deaths from IS [54]. In the long-term follow-up conducted by the Canadian Paediatric Ischaemic Stroke Registry, 67% of children surviving an AIS had neurological deficits. Hemiparesis was observed in 55–62% of patients after AIS [55].
A significant predictor of outcome was age: neonates had more favourable outcomes than older children [10]. In contrast, neonates are more frequently affected by post-discharge seizures (17% of cases) [10]. In a Polish cohort study of paediatric patients who had suffered from AIS, young age at the time of AIS, presence of focal cerebral arteriopathy, and total anterior circulation infarct stroke subtype were indicated as predictors of late seizures (between seven days and two years after AIS onset), and of the development of post-stroke epilepsy. All late remote seizures evolved into epilepsy [56].

Paediatric patients are distinctly more vulnerable to post-stroke seizures than adults [57]. In a retrospective population-based study of children with stroke, the average annual incidence rate of a first remote seizure post-stroke was 4.4%, with a 5-year cumulative risk of 16% and a 10-year cumulative risk of 33%. The cumulative risk of active epilepsy (anti-convulsant treatment for remote seizure within the previous six months) among children with acute seizures was 25% by the age of five years. Predictors for development of post-stroke seizures were younger age and the presence of acute seizures at the time of stroke. According to a British cohort study, the greatest risk for a first remote seizure was within the first year after stroke [58]. Therefore, a post-stroke paediatric patient should be cautiously monitored for seizures in order to facilitate early treatment by drugs or surgical treatment and improve cognitive development, motor skills and quality of life.

In addition to motor functions, other domains can also be affected, i.e. vision, speech, cognitive skills, and behaviour [59, 60]. Paediatric stroke may affect the intellectual and behavioural development of a child. In addition, attention, intellectual and executive functions may be impaired by AIS [61]. Among paediatric patients who had HS, in a study of 19 children, mild to lower quality of life, compared to normative means, was described in the majority of survivors [62]. According to a Swiss study, 21% of patients who experienced AIS during childhood had language difficulties, and among them 6% had severe impairment. As long term outcomes, impaired balance and visual disturbances are also indicated [63]. It is important to acknowledge that further neurological deficits can emerge with a child’s development. Consequently, a long-term follow-up is needed.

Recurrent stroke is a significant problem in the paediatric population and poses a risk of further impairment. In the study by Fullerton et al., 16% of children suffered a recurrent ischaemic event (stroke or TIA) during the follow-up period. The cumulative rate of the first recurrence of a stroke amounted to 6.8% at one month and 12% at one year [64]. In another study, 77% of recurrent AIS occurred within the first six months after the first AIS [65].

Summary

The awareness of paediatric stroke is inadequate, both in society generally and more alarmingly among clinicians. Medical associations have tried to influence society and medical communities have devised social campaigns like B.E. F.A.S.T. for Kids created by the International Alliance for Paediatric Stroke.

Childhood stroke requires a high level of awareness among first-line healthcare providers. The aim is to decrease the time between the first symptoms and the AIS diagnosis in order to facilitate clinical attempts at treatment with t-PA and thrombectomy.

Both t-PA and thrombectomy treatments are not registered in children. Therefore, they should be considered very carefully and only carried out in medical centres of high reference with an experienced team of neurosurgeons and neurologists. Unfavourable trials should always be taken into consideration in order to ensure patient safety.

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