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Be aware of childhood stroke: Proceedings from EPNS Webinar

Gabriela Oesch [a,1], Robin Münger [a,b,1], Maja Steinlin [a,*]

[a] Division of Neuropaediatrics, Development and Rehabilitation, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b] Graduate School for Health Sciences, University of Bern, Switzerland

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ABSTRACT

Childhood arterial ischaemic stroke (AIS) is a significant health concern with increasing incidence. This review aims to provide an overview of the current understanding of childhood AIS.

The incidence of childhood AIS is on the rise especially in developing countries, likely due to improved awareness and diagnostic capabilities. Aetiology of childhood AIS is multifactorial, with both modifiable risk factors and genetic predisposition playing important roles. Identifying and addressing these risk factors, such as infection, sickle cell disease, and congenital heart defects, is essential in prevention and management. Identifying underlying conditions through genetic testing is important for appropriate management and long-term prognosis.

Clinically, distinguishing stroke from stroke mimics can be challenging. Awareness of important stroke mimics, including migraines, seizures, and metabolic disorders, is crucial to avoid misdiagnosis and ensure appropriate treatment. The diagnostic approach to childhood AIS involves a comprehensive "chain of care," including initial assessment, neuroimaging, and laboratory investigations. National guidelines play a pivotal role in standardizing and streamlining the diagnostic process, ensuring prompt and accurate management.

Early intervention is critical in the management of childhood AIS. Due to the critical time window, the question if mechanical thrombectomy is feasible and beneficial should be addressed as fast as possible. Early initiation of antiplatelet or anticoagulation therapy and, in select cases, thrombolysis can help restore blood flow and minimize long-term neurological damage. Additionally, rehabilitation should start as soon as possible to optimize recovery and improve functional outcomes.

In conclusion, childhood AIS is a growing concern. Understanding the increasing incidence, age distribution, risk factors, clinical presentation, diagnostic approach, and management strategies is crucial for optimized management of these patients.

1. Introduction and definition

Reflecting the important progress in treatment options for adult patients with arterial cerebrovascular insult, there is also an increased awareness of paediatric stroke. This is shown by a tenfold increase of yearly publications on the topic over the last 30 years.

Paediatric stroke summarizes arterial ischaemic and haemorrhagic stroke from the prenatal period up to the end of adolescence. Sinus venous thrombosis can lead to stroke in rare cases, but does not generally fall under this definition per se. Perinatal stroke takes place in children aged up to 28 days of life including the subgroup of neonatal stroke (defined by becoming symptomatic during the neonatal period). In addition, there are prenatal strokes happening during pregnancy not related to the birth process. This review will only cover the topic of arterial ischaemic stroke (AIS) during childhood (from 29 days until 16 years).

2. Epidemiology

2.1. Incidence

Reports about incidence rates of childhood stroke show wide variability. Differences in age ranges and definitions of included events make direct comparison difficult.

Data mainly exist for high income countries for which incidence rates of around 2:100′000 children per year for AIS in the age group up to 16 years/18 years have been reported with a range between 0.58 and 7.9/

* Corresponding author. Division of Neuropediatrics, Development and Rehabilitation, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland.
E-mail address: maja.steinlin@insel.ch (M. Steinlin).
[1] Gabriela Oesch and Robin Münger contributed equally to this work.

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Non-standard abbreviations and acronyms

ADA2	Adenosine deaminase 2
AGS	Aicardi- Goutières Syndrome
AIS	Arterial ischemic Stroke
BA	Basilar artery
CIMT	Constraint-induced movement therapy
CMV	Cytomegaly virus
CT	Computer Tomography
DALY	Disability Adjusted Life-Years
DOACS	Direct Oral Anticoagulants
EBV	Epstein-Barr Virus
EEG	Electro Encephalogram
FCA	Focal Cerebral Arteriopathy
FCA-d	Focal Cerebral Arteriopathy with intracranial arterial dissection
FCA-i	Inflammatory Focal Cerebral Arteriopathy
FOCAS	Focal Cerebral Arteriopathy Steroid Trial
HSV	Herpes simplex virus
ICP	Intracranial pressure
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
NF1	Neurobibromatosis type 1
NIRS	Near-infrared spectroscopy
PASTA	Pediatric Arteriopathy Steroid Aspirin Trial
pedNIHSS	Paediatric National Institute of Health stroke scale
SNPSR	Swiss Neuropaediatric Stroke Registry
tPA	Tissue Plasminogen Activator
TTP	Thrombotic Thrombocytopenic purpura
VZV	Varicella Zoster Virus

100′000 children per year [1–8]. A burden of disease study from 2015 has shown an increasing prevalence in developing, but also in developed countries from 1990 to 2013- this is attributed to increased population, increased recognition but also increased survival of diseases leading to stroke [9].

There are three age peaks of childhood stroke [6,8,10,11]: The first during the first two years of life, which is attributed to children with congenital heart problems who will have most of their investigations and operations during infancy. The second peak finds place in preschool age and is likely reflected by the parainfectious/infectious triggers for stroke and the fact that children in this age group undergo many infections. The third peak is in adolescence and likely reflects the group of children suffering other systemic diseases with stroke as complication.

2.2. Risk factors

In almost all studies boys are more affected than girls, the reason for this is still not fully understood [2,10,12].

Worldwide, sickle cell disease is the most common cause of stroke in childhood. It is associated with a higher recurrence and mortality rate than in children without sickle cell disease [4,13–15]. This explains partially but not completely the increased risk for ischaemic stroke in sub-Saharan children. However, the aetiology may differ according to local epidemiology and ethnic diversity. Literature describes almost a doubled risk for black compared to white children and approximately the same risk for children of Asian descent compared to white ones. Hispanic children have a lower incidence of arterial ischaemic stroke [2,10,16,17].

Infections, trauma and radiotherapy for head and neck cancer account for the most important acquired risk factors [18–24].

3. Diagnosis

3.1. Clinical symptoms

Stroke in children should be considered in every patient presenting with a new (focal) neurological deficit. The most frequent clinical sign of childhood stroke is hemiplegia (with or without facial palsy) in 60–80% of children [6,25,26] which is slightly less frequent than in adulthood (>80%) [27]. Speech problems, especially dysarthria and dysphasia, can be detected in 30 up to 75% in the acute phase after AIS [6,28]. In the study of Liégeois et al. arterial territory was not a predictor of dysarthria or speech impairment in children aged between 3 and 17 years [28]. It is very important to realize that dysarthria or dysphasia may also appear in case of stroke in the non-dominant hemisphere. The high percentage of dysarthria or speech impairment in paediatric stroke patients compared to adults (24%) [27] might be explained by the wider language networks existing in the immature brain [28].

Epileptic seizures are common in childhood stroke, especially in younger children. Around 20–30% of children suffer an epileptic seizure during the acute phase of stroke, whereby most of the seizures occur within the first 24 h after stroke onset [21,25,29]. Status epilepticus is common in infants [29]. Non-localizing symptoms like headaches (in 20–40%) and vertigo are present in AIS [6], the latter especially in stroke of the posterior circulation, however, are more common in haemorrhagic stroke [30].

The assessment of clinical symptom severity is performed with the paediatric NIH stroke scale (pedNIHSS) [31]. This score should be administered at arrival as soon as possible, on a regular basis during the acute phase of investigations as measure of clinical course as well as during the first days of rehabilitation. A progression and recurrence of symptoms, respectively, after acute onset of stroke is typically associated with stenotic intracerebral arteriopathies [32].

In addition, careful clinical examination is mandatory in each stroke patient as there might be clues to the underlying aetiology. Changes might be detected on the skin (café au lait-spots in neurofibromatosis type 1, Fabry disease, embolic pathologies), hyperextensible joints might point to a collagen defect as well as possible dissection and morning glory disc in association with AIS is suggestive for Moyamoya angiopathy [33,34]. In addition, clinical history might reveal underlying pathologies: Transient ischaemic attacks can point to Moyamoya disease. After recent trauma search for dissection, in case of antecedent viral illness diagnostics for focal cerebral arteriopathy and in case of unexplained syncope and shortness of breath search for cardiac problems are essential.

3.2. Stroke mimics and diagnostic approach

In paediatric patients' diagnosis and accordingly treatment of stroke is often delayed because of unspecific first clinical signs, especially in very young children [35]. The most frequent mimics on arrival on the emergency department are migraine, seizures, and Bell's palsy [36]. The list of stroke mimics is long, including demyelinating syndrome, infection and tumour. Although awareness of stroke increased over the last decade, publications from the last 20 years analysing time lag of childhood stroke diagnosis show that only 20–30% of children are diagnosed within the first 6 h [35,37,38].

Clinical screening tests as "FAST" show similar sensitivity in children compared to adults. Like adults, the sensitivity for posterior circulation stroke can be improved if the "FAST" test is extended to "beFAST", adding "balance" and "eyes" to the initial assessment [39]. However, due to stroke mimics they are not very specific why emergency imaging is crucial in any child with suspicion of stroke. The gold standard is magnetic resonance imaging (MRI) within the first hour after

presentation. A proposed algorithm for neuro-imaging in paediatric patients with suspected stroke is shown in Fig. 1 [40]. Image 1 shows the results of MRI imaging in an acute arterial ischemic stroke of a 9 year old boy due to a P2 occlusion. Further diagnostic work-up is depicted in Fig. 2a and b.

It is crucial for any emergency setting to have a stroke protocol in place on how to proceed in case of suspected stroke. National guidelines emphasize the most important steps to consider in the chain of care for children with stroke:

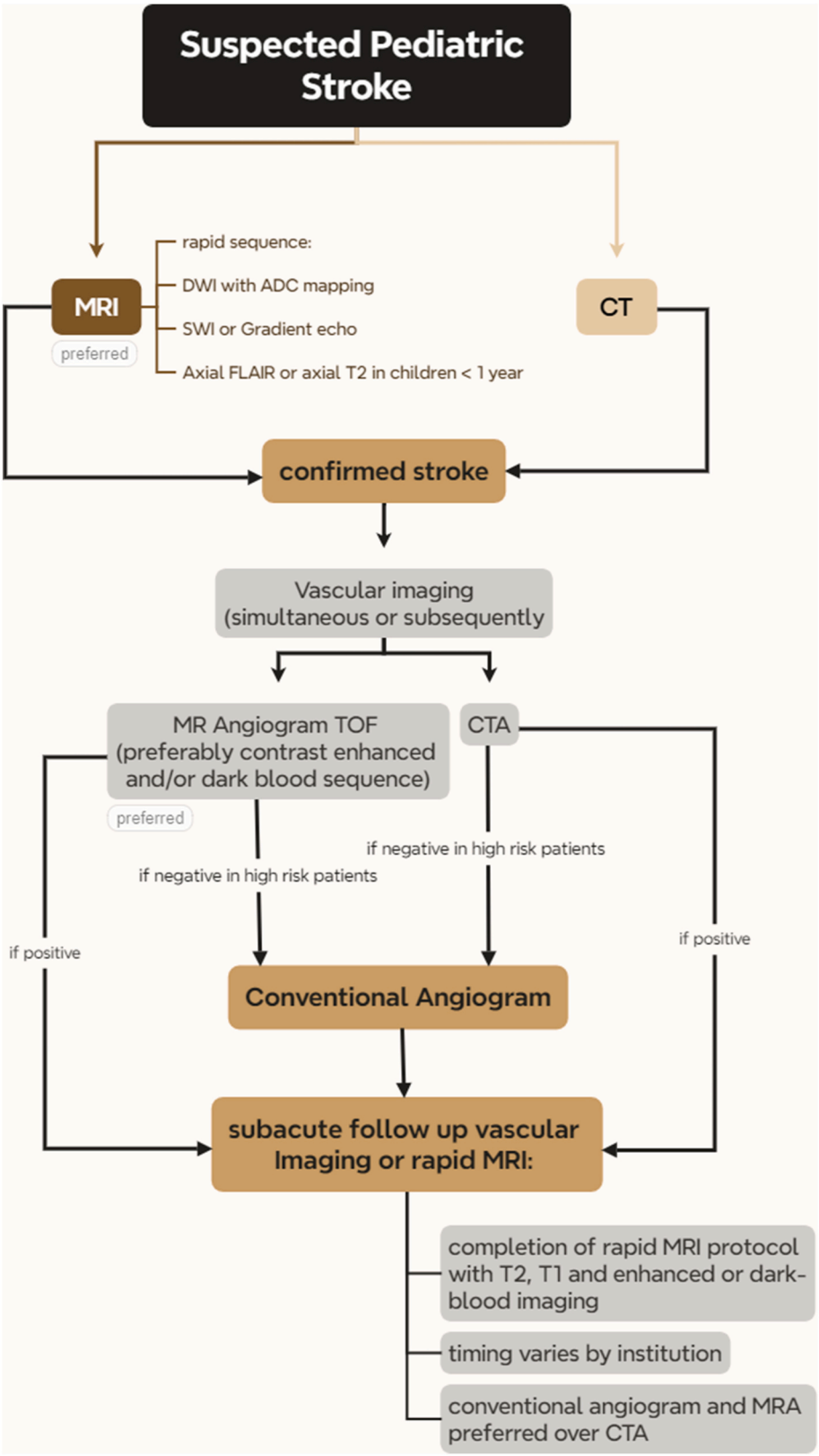

Fig. 1. Diagnostic imaging algorithm in paediatric AIS, adapted from Khalaf et al. [40].

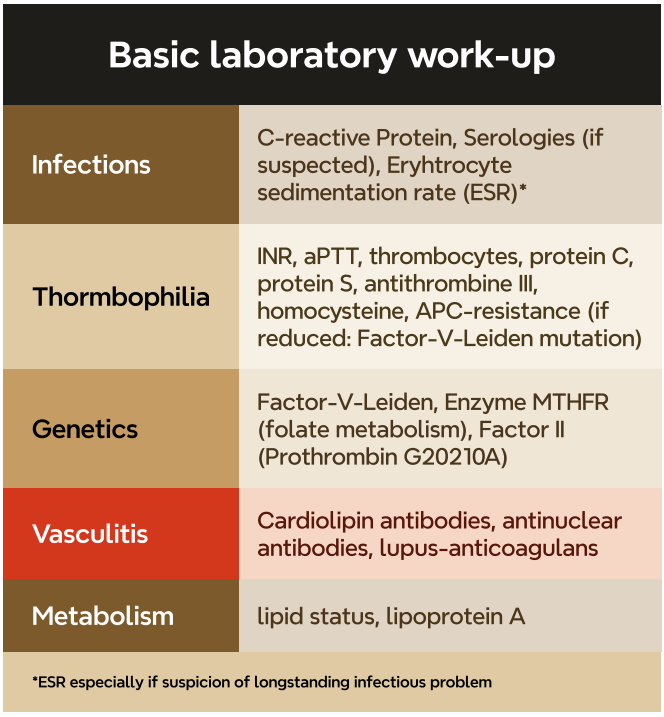

Fig. 2a. Basic diagnostic laboratory work-up in paediatric AIS.

- Who takes care of these children, is taken care locally or is the child sent on to a paediatric stroke centre?
- Which imaging modality (CT scan or MRI) and which modality of sedation should be performed and how to achieve it within an hour of the child's arrival?
- Who is responsible for taking decisions upon neuroimaging the paediatric neurologist or the stroke neurologist (a joint approach is likely the best in many situations)?
- Who will perform thrombolysis or thrombectomy if indicated?
- Who takes decisions on treating stroke in the subacute situation and where will the child be looked after (intensive care unit, stroke unit)?
- Which investigations must be considered and who takes care for proper rehabilitation of the patient?

4. Aetiology

While arteriosclerosis is an important risk factor in adult AIS [41], aetiology of childhood stroke is very different to adults and regarded as interplay between genetic and environmental risk factors [42]. Aetiologies of childhood stroke are summarized in Fig. 3. Besides the primary underlying categorization of acute onset stroke, chronic course of arteriopathic AIS is classified into progressive, stable, reversible and indeterminant.

Usually, aetiology is multifactorial with important trigger or risk factors leading to cerebrovascular insult. The VIPS study proved that an infection within the prior week is an independent trigger for AIS in children [44]. A positive serology for subacute herpes virus infection doubles the risk of stroke – yet, herpes infection often is not clinically manifest [45]. There are other important acquired risk factors for childhood stroke: Head and neck trauma, common in the paediatric population, may trigger stroke with a short to medium delay. In contrast, rare trigger factors as radiation therapy or cancer of the head/neck affecting a specific small subpopulation represent a long-lasting risk for arterial ischaemic stroke [20,42].

Prothrombotic disorders (e.g., Factor V Leiden, increased lipoprotein A) may be a predisposition to trigger stroke in children, especially in combination with concomitant infections. Other familiar/genetic risk factors will be discussed in the section "genetic causes".

4.1. Heart disease

About 30% of all childhood strokes are provoked by cardioembolic pathology [46]. Children with cyanotic congenital heart disease are at highest risk for AIS during the periprocedural period (cardiac catheterization and cardiac surgery) [47]. Asakai et al. as well as Henzi et al showed median age at stroke of these children to be at 5 months [48,49]. This early age peak is explained by the fact that these patients undergo interventional investigations and (open) heart operation at an early age. Risk factors to suffer stroke are foreign cardiac material, arterial hypotension and/or low cardiac output in the periprocedural period as well as infections [49]. Moreover, about one-fifth of children undergoing treatment with ventricular assist devices suffer ischaemic or haemorrhagic strokes [50,51].

Cardioembolic paediatric stroke is more often located in the anterior circulation while up to 37% of all childhood strokes affect the posterior circulation, mostly due to intracranial arteriopathies [52].

Acquired heart disease as endo-myocarditis, cardiomyopathy or arrythmias are associated with stroke in only 20% [49].

Unfortunately, children with cardiac pathology show a delay of stroke diagnosis from up to 4 days-despite being frequently under close supervision at intensive care units. Nevertheless, this fact may be related to sedation in the cardiac ICU and therefore limiting possibility for thorough neurological examination [49]. As they are candidates for endovascular treatment a more intense observation (as continuous EEG, NIRS) should be discussed in high-risk patients shortly before and after procedural interventions.

4.2. Arteriopathies

In a large international paediatric stroke cohort study (725 children) 34% suffered from a stroke due to arteriopathy, 27% had dissection, 24.5% Moyamoya angiopathy, 15% focal cerebral arteriopathy of inflammatory type, 15% diffuse vasculitis and 18.5% unspecific arteriopathies [53]. Current studies show different data about distribution of arteriopathy subtypes which is likely explained by the influence of different cultural populations like sickle cell disease in Sub-Saharan Africa or the increasing number of Moyamoya angiopathy in the Asian population.

4.3. Focal cerebral arteriopathy of childhood

Focal cerebral arteriopathy (FCA) was originally defined as unifocal and unilateral stenosis/irregularity of the large intracranial arteries of the anterior circulation [54]. As there are also reported cases of FCA within the posterior cerebral blood supply the definition has to be expanded to the posterior circulation [55,56]. FCA dissection type (FCA-d) and inflammatory focal cerebral arteriopathy (FCA-i) are the most frequent focal vasculopathies in children provoking stroke [54]. FCA-i refers to presumably inflammatory changes and stands for a focal vasculitis with parainfectious pathophysiology. The common understanding is that an inflammatory process leads to vessel wall inflammation and swelling (as shown by local arterial wall enhancement in MR-black blood sequences) which provokes stenosis, thrombosis at the level of stenosis, and maybe arterial vasospasm [32]. Stroke occurs either due to the diminished or stopped blood flow or due to small emboli streaming into the periphery of the affected vessel. The latter pathophysiology also explains the often-observed stuttering onset of symptoms. The best-known virus provoking FCA-i is Varicella zoster virus (VZV). Varicella zoster virus stays primarily in the trigeminal ganglion in a latency stage, then will be activated and wandering via afferent fibres to the circle of Willis. Experiments show that VZV is also latent in the superior cervical ganglion spreading to the vessels within the posterior circulation responsible for FCA-i of the posterior

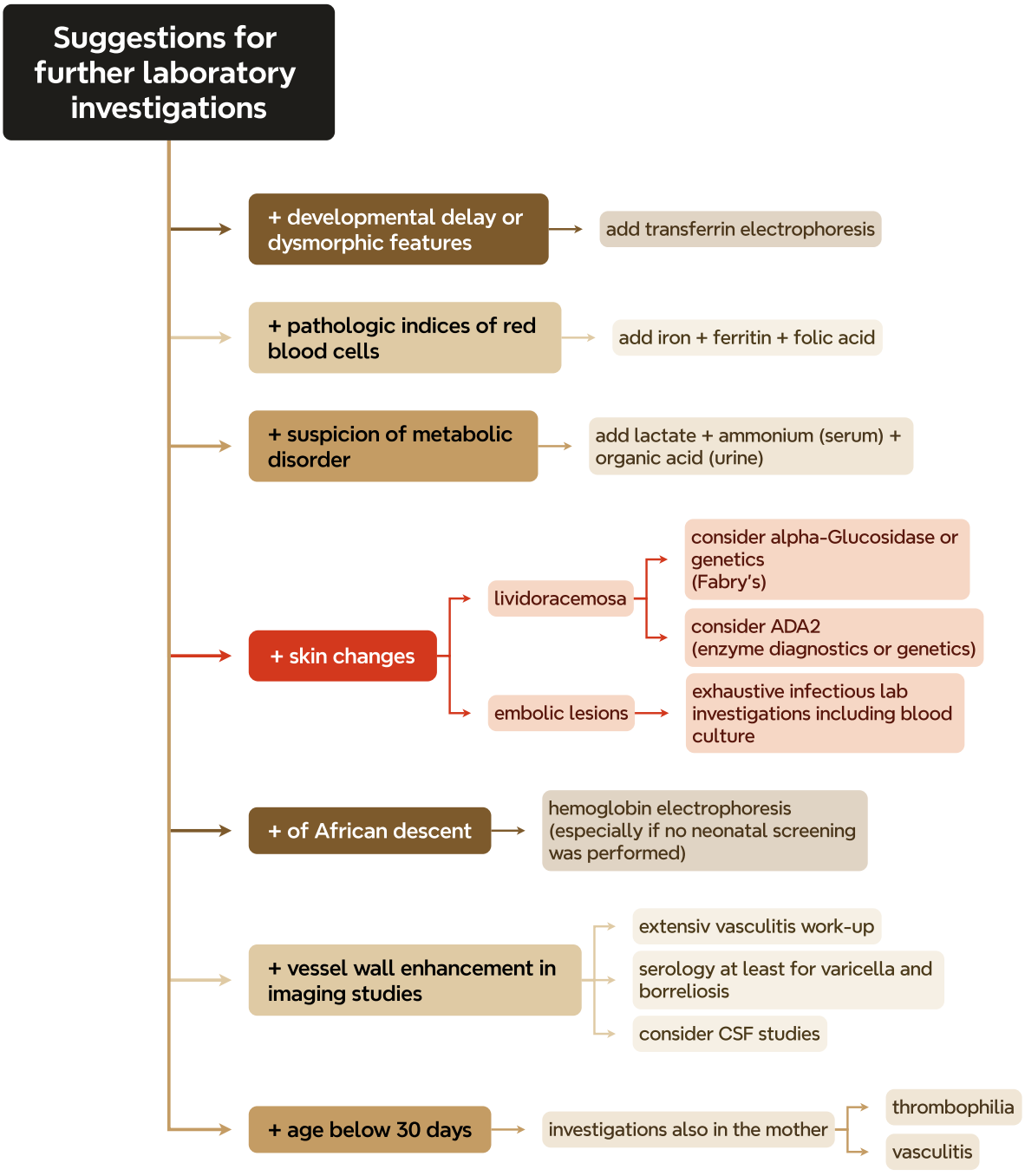

Fig. 2b. Suggestions further laboratory investigations in paediatric AIS.

circulation. In addition, mild FCA-i in the posterior circulation may be associated with vertebrobasilar arteriopathy or dissection [57].

Many other pathogens are associated with FCA-i like other herpesviruses (HSV1 and 2, CMV, EBV), parvovirus B19 and SARS-CoV-2 [58,59]. Dengue fever caused by arboviral infection has also been associated with paediatric AIS due to vasculitis [60]. COVID-19 infection is related to AIS in children; however, pathophysiology is not fully understood yet [58].

Borrelia burgdorferi is associated with paediatric stroke in only 2% of all childhood AIS [61]. Thereby the posterior circulation seems to be especially affected by a multifocal vasculitis leading to cerebrovascular insult [61].

Imaging patterns are discussed to distinguish between the different cerebral arteriopathy types which most probably represent a spectrum rather than different entities (especially FCA-i and FCA-d). Vessel wall imaging came into light in the last decade and might be helpful for differentiation. Yet, its role as biomarker for the differential diagnosis and clinical course of FCA remains controversial [62,63]. In paediatric stroke due to FCA-i MR angiogram is the crucial diagnostic tool showing a swelling, also called banding, of the affected vessel leading to stenosis as can be seen in the image 2.

FCA-i is usually a monophasic problem, with initial worsening followed by decrease of stenosis, and does not progress after 6 months of stroke onset. The course of disease in FCA-i related stroke is associated with first worsening of the arteriopathy followed by slow improvement-about 24% show complete remission, 45% improvement and 32% stabilisation [64].

Image 2 shows an FCA affecting the left anterior circulation with

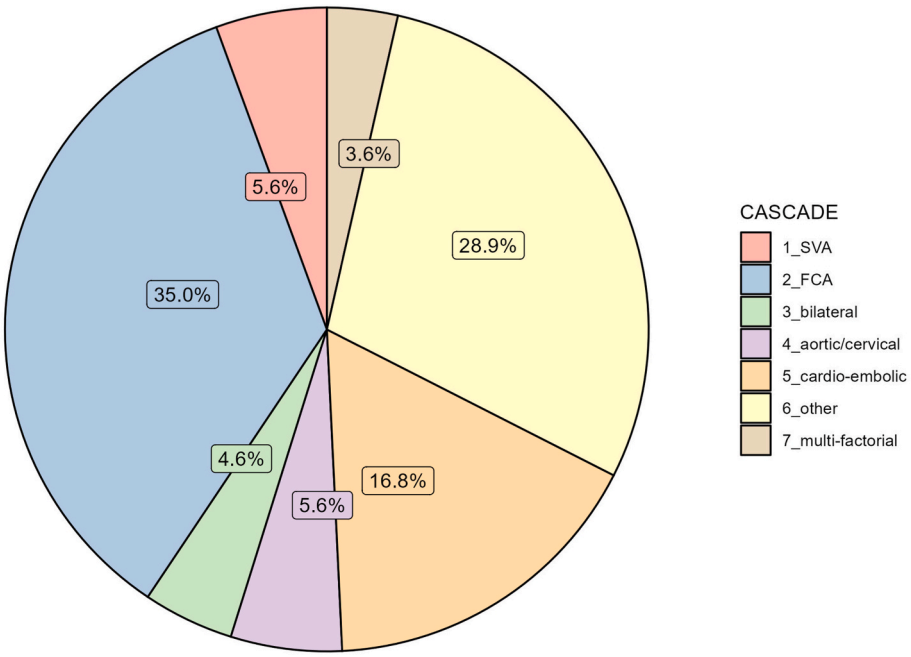

Fig. 3. Common aetiologies of childhood arterial ischaemic stroke based on the CASCADE criteria [43], data from the Swiss Neuropaediatric Stroke Registry (SNPSR) between January 2000 and August 2021. 1 = small vessel arteriopathy, 2 = focal cerebral arteriopathy of childhood, 3 = bilateral cerebral arteriopathy of childhood, 4 = aortic/cervical arteriopathy.

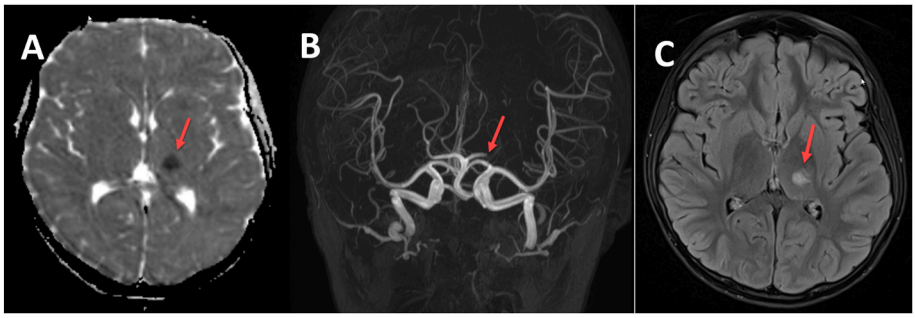

Image 1. Acute Stroke in 9-year-old boy due to left P2 occlusion. A) acute diffusion imaging with ADC 8 h after symptom onset showing diffusion restriction in left posterior internal capsule and left posterior thalamus, B) TOF angiogram 8 h after symptom onset showing left P2 occlusion, C) FLAIR demarcation 30 h after symptom onset.

>50% stenosis of left supraclinoid internal carotid artery (ICA), < 50% stenosis of the M1 segment of the middle cerebral artery and banding of the A1 segment of the anterior cerebral artery (arrows).

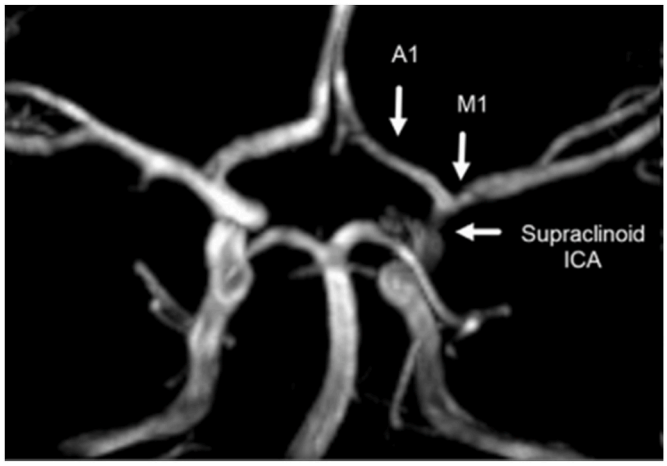

Image 2.

4.4. Arterial dissection

The mechanism of AIS in children due to arterial dissection is still poorly understood [42]. It is more common in boys than in girls-not explained by a higher rate of trauma in boys compared to girls [65]. Besides spontaneous cases, dissection is associated with (genetic) diseases of the soft tissue as well as with previous trauma. In many cases aetiology of dissection remains unclear and might be associated with arteriopathic changes which led to the distinction of focal cerebral arteriopathy (FCA) FCA-i (infectious) and FCA-d (dissection) type [54]. As reported in a review, in paediatric arterial dissection within the posterior circulation the extracranial part of the vertebral arteries is the most common anatomic site. Within the anterior circulation, however, dissection happens more often in the intracranial parts of the carotid arteries, as exemplary shown in image 3 [65].

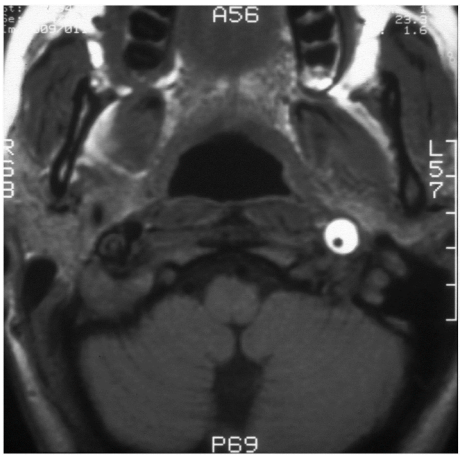

Image 3. Dissection of the left Internal carotid arteries.

4.5. Moyamoya angiopathy

Moyamoya angiopathy, a rare progressive arteriopathy, was first described in 1957 [66]. Moyamoya means "something hazy, like a puff of cigarette smoke" in Japanese and describes the characteristic net of collaterals compensating for the reduced blood flow in the cerebral circulation. Moyamoya disease is defined as uni- or bilateral progressive stenosis of the distal internal carotid arteries and/or their proximal branches. Moyamoya syndrome, in contrast, is defined as Moyamoya angiopathy associated with well-defined other conditions such as neurofibromatosis type 1, Down syndrome, sickle cell anaemia and others [67]. Moyamoya angiopathy is likely to start anterior but does also affect the posterior circulation. The disorder is most common in East Asia with an increasing incidence rate of 0.9–4.3/100′000 inhabitants over the last decade [68]. Incidence in children is reported to be lower at around 0.18/100′000 between 2016 and 2018 [69]. Clinical presentation of Moyamoya consists of sudden mostly ischaemic stroke, transient ischaemic attacks or migraine (common in children) with high risk of stroke recurrence [67].

In Moyamoya the occlusion of a cerebral vessel leads to a local perfusion deficit and the development of collaterals. If the collaterals are insufficient, the patient develops migraine, TIA or strokes.

The stenosis or occlusion of the vessel is thought to be caused by intimal smooth muscle cell proliferation. While the molecular mechanisms are unknown, an emerging number of gene variants have been associated with Moyamoya. Currently, there are 16 genes involved in Moyamoya-angiopathy with RNF213 being the most prominent one, especially in the Asian population [70]. While RNF213 is regarded as susceptibility gene for Moyamoya with low penetrance there is increasing evidence that Myamoya angiopathy is associated with infections and autoimmune diseases [68]. In this context recent studies discovered a very important antimicrobial function of the RNF213 protein suggesting that infection or immunological stimulus might act as second hit in the pathogenesis of Moyamoya angiopathy [68,71].

Besides starting with aspirin, the only treatment option of Moyamoya angiopathy to date is direct or indirect re-vascularisation surgery [67,72].

4.6. Genetic causes

To date, the list of candidate genes for paediatric stroke is still short.

Mutations in RNF213, ACTA2, ADA2 and MYH11 cause occlusive vasculopathy by damaged vascular smooth muscle cell layer and endothelium, respectively, showing a Moyamoya or Moyamoya-like clinical phenotype. Especially ACTA2 is associated with a strong age-dependent penetration [73,74]. Heterozygous ACTA2 mutation causes enlarged proximal parts of the carotid artery followed by an occlusive disease of the distal vessels without collaterals. Intracranial arteries show an abnormal straight appearance as shown in Image 4 [75]. Hence, neuroimaging findings in ACTA 2 are almost pathognomonic. In addition, ACTA 2 might be associated with persistent mydriasis or other smooth muscle cell dysfunction like patent ductus arteriosus or pulmonary hypertension [75].

4.7. Small-vessel disease/vasculitis

ADA2 (Adenosine deaminase 2), mentioned already above, is another genetic multisystem disorder associated with typically small lacunar ischaemic stroke, but some patients also suffer from haemorrhagic stroke. The disease is associated with small-vessel vasculitis [76].

Autosomal dominant mutations in COL4A1 and COL4A2 encoding type 4 collagen, a structural component of the basement membrane, can cause cerebral small-vessel disease and ischaemic or haemorrhagic stroke in children [77].

4.8. Vascular degeneration, cerebral white matter

CADASIL syndrome, caused by autosomal dominant mutations in NOTCH3, is characterized by vascular degeneration primarily in the cerebral white mater. The clinical picture and white mater changes in CARASIL are like those in CADASIL. It is very rare and caused by autosomal recessive mutations in the HTRA1-gene [78]. Neither CADASIL nor CARASIL are likely to manifest in childhood and are rather an adult disease.

Beside these monogenic variants associated with stroke there is an increasing number of syndromic multisystem disorders with stroke as an important clinical manifestation: About 6% of children with neurofibromatosis type 1 (NF1) and 39% with Alagille syndrome suffer from arteriopathy leading to stroke [79,80]. Grange syndrome and sickle cell disease are also associated with cerebrovascular insult [14,81]. Aicardi-Goutières Syndrome (AGS) due to variants in TREX1 may be challenging to diagnose as its clinical picture covers a wide range of clinical signs with multi-system involvement and recurrent ischaemic stroke as possible first clinical sign [82]. X-linked Fabry disease covers a wide clinical spectrum and can be treated by enzyme replacement therapy [77]. Finally, ADAMTS13 variants cause hereditary thrombotic thrombocytopenic purpura (TTP) also known as Upshaw-Schulman syndrome. Homozygous variants result in severely deficient ADAMTS13 enzymatic activity provoking cerebrovascular ischemic events due to thrombotic microangiopathy [83].

5. Treatment

To date there are no established guidelines for optimal treatment of

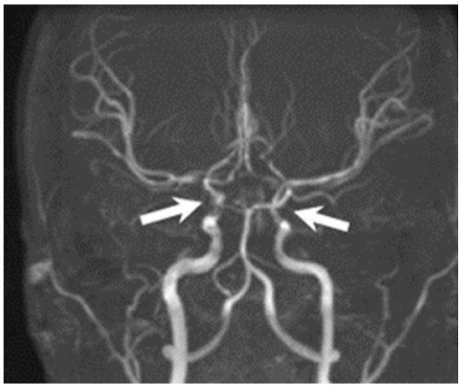

Image 4. ACTA2 Vasculopathy with the dilation of the internal carotid artery to stenoocclusion.

childhood AIS and most recommendations are based on the experience gathered in adult patients or other paediatric diseases [84].

5.1. Basic management

For any child with an acute infarction the rule of basic support concerning ABC should be provided – most importantly to assure a (high) normal oxygen saturation as well as a normal to high blood pressure. As it is shown in adults with stroke or children after traumatic brain injury, normothermia and normoglycemia support recovery and should be targeted [11,84–86]. In children with large AIS monitoring of intracranial pressure (ICP) should be evaluated. However, in case of malignant AIS and risk of herniation quick decompressive craniectomy must be performed and surgery not delayed by installation of ICP monitoring beforehand [84,87]. Image 5 shows a left sided malignant AIS before and after decompressive craniectomy. If ICP is monitored, maintaining it below 20 mmHg is necessary, and the use of hypertonic saline or mannitol is recommended [88].

About 20% of children suffer an epileptic seizure during the first few days, thus close clinical monitoring with a low threshold for EEG monitoring should be provided. Seizures should be treated immediately with antiepileptic drugs. However, a systematic prophylactic antiepileptic treatment over days or weeks to avoid further seizures is often not necessary [29,89].

5.2. Hyperacute management

Until today no successful trials on hyperacute management of children presenting with stroke on the use of thrombolytics or endovascular thrombectomy could be completed [90,91]. But evaluations of paediatric stroke centres with clinical expertise and access to rapid stroke neuro-imaging show that these treatment options with the right setting in place are feasible within an appropriate time frame [92–94]. Further, case series provide evidence that acute recanalization therapy (including thrombolytics and endovascular thrombectomy) has no higher risk then in adults and might be of benefit also for children [95–100].

Due to the lack of randomized controlled trials, there is currently no approval for intravenous tissue-type plasminogen activator (tPA) in children. Consensus statements suggest the use of intravenous thrombolytics in a subgroup of patients and that the dose regimen should follow adult dose regimens of 0.9 mg/kg [84,101].

A multicentre observational study from 27 centres across Europe and the United States including 73 cases of patients with ischaemic stroke who underwent endovascular recanalization showed that the safety profile of thrombectomy in childhood stroke does not differ from the safety profile in randomized clinical trials for adults [102] and a follow up-study even found evidence that a subgroup of children might be eligible for thrombectomy more than 6 h after stroke onset [103]. In a large meta-analysis including 11 studies and 215 children the successful recanalization rate was 90%, complete recanalization in 53%. Favourable outcome (MRS 0–2) was 85% [104]. These data support that thrombectomy should be considered in children – although a reporting bias from successful cases cannot be excluded. In addition, there is still the uncertainty which children will profit from thrombectomy. Age of the child, underlying aetiologies, data from acute perfusion studies, collateral integrity and clinical diffusion mismatch might help in this decision [102,103,105,106]. Further analysis suggests that cost-effectiveness of thrombectomy in childhood AIS is likely [107].

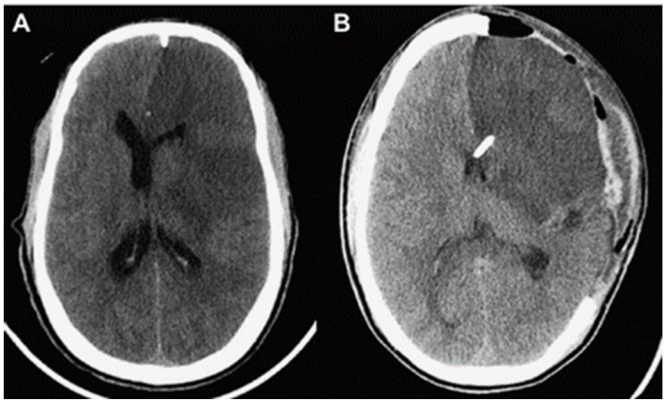

Image 5. A) malignant infarction of the left hemisphere with compression of the left ventricle and midline shift. B) same patient after decompressive craniectomy on the left side.

5.3. Anticoagulation

There are no studies to answer the question whether antiplatelet or anticoagulation treatments are the better choice in the acute setting. For most of the indications immediate start of treatment with aspirin (3–5 mg/kg BW in the acute phase) is considered the first choice [84,108,109]. Anticoagulation with heparin should be evaluated in cases with embolic (heart) problems or dissection. However, studies in children with congenital heart defect [110] and study in dissections in adults [111] do question the need of a heparin or low molecular weight heparin treatment in these children. The role of direct oral anticoagulants (DOACS) in acute childhood stroke is not yet decided. After an acute recanalization treatment, the local protocol for start of antithrombotic treatment should be followed.

For long-term prophylaxis aspirin in a dosage of 3 mg/kg BW is the best choice. Duration of treatment is not evident and underlying problem have to be taken in account. Most specialists treat for at least 2 years and then re-evaluate the situation [84,108]. In case of residual arteriopathy a lifelong treatment should be discussed. In addition, it is important for these children and adolescents to monitor carefully the risk factors for cardiovascular problems in adulthood.

5.4. Special indications

5.4.1. FCA-inflammatory type

Treatment with aspirin to decrease the amount of thrombotic or embolic events is the first choice. Thrombectomy should be discussed very critically, as there are usually no or small thrombi and the risk to injure the inflammatory vessel wall is not to neglect [97,102]. Steroids to decrease the swelling and inflammatory process are increasingly used [112]. Evidence for that is now searched in two parallel studies (PASTA in Europe and Australia [113] and FOCAS in North America [114]).

5.4.2. Moyamoya

For children with Moyamoya disease or syndrome good monitoring of body fluid and blood pressure is important (target up to 90th percentile for systolic pressure for age) [115] to improve blood circulation in the brain. These children will need an evaluation for surgical revascularization [116–119]. Whether direct surgery or indirect revascularization is preferred has to be decided individually based on results from brain MRI, MR perfusion studies and six vessel angiography as well as intraoperative Doppler. Patients with Moyamoya have an increased risk of complications in anaesthesia, and an experienced team should take care for them. Long-term antiplatelet therapy with aspirin after surgery is often indicated [115].

5.4.3. Sickle cell disease

Blood transfusion with a goal of haemoglobin S ratio <30% (haemoglobin values of 10 g/dl) should be started as soon as stroke is suspected. If haemoglobin is > 11 g/dl exchange transfusion aiming for haemoglobin S concentration of 15% is recommended. Despite data from a recent meta-analysis showing that the level evidence for primary

or secondary stroke prevention with red blood cell transfusions or hydroxyurea remains low [120], international guidelines strongly recommend monthly exchange transfusions after paediatric stroke in SCD [121].

6. Rehabilitation

Rehabilitation should start as fast as possible. Most prominent improvement takes place in the first 3–6 months [122]. In the first few days, careful mobilization is important to assure that blood circulation in the brain is sufficient and no worsening of symptoms will take place during activities. During these days it is also important to have a thorough evaluation of the problems - neuromotor problems, speech and swallowing problems as well as neurocognitive weaknesses. The stroke rehabilitation team should include specialists like specialized paediatricians, occupational therapists, physical therapists, speech-language pathologists, nurses, social workers, psychologists and dietitians. Typical therapies include range of motion exercises, hand and wrist splints, traditional or modified constraint-induced movement therapy (CIMT), functional electrostimulation, mirror therapy, chemodenervation using Botulinum Toxin Type A, repetitive transcranial magnetic stimulation and surgical interventions [123].

7. Outcome

For many decades outcome of children was thought to be superior compared to adults. However, the belief in plasticity of the child's brain must be rediscussed [124,125]. Many studies show that concerning outcome a lesion in a developing network might be worse than in a fully developed system [126]. Children have similar outcome compared to young adults [127,128].

7.1. Mortality

An analysis of mortality in childhood stroke in England and Wales between 1921 and 2000 showed a steady decline from the 1960s onward [129]. Mortality rates of AIS have dropped from up to 18% in the 1980s to around 6–9% in the early 2000s [1,2,6,130]. A population-based study in 2012 reported an overall fatality rate of 4% which was similar for ischaemic and haemorrhagic stroke [131]. A global burden of disease analysis in 2015 showed a marked decrease in death and disability adjusted life-years (DALY) between 1990 and 2013 in developed countries. The burden of stroke was significantly higher in developing countries and in men (especially in adolescents) compared to women [132].

7.2. Morbidity

About 2/3 of children with AIS present with motor hemiparesis, and almost half of all still show symptoms after 6 months. Similar improvement rates of about 1/3 are seen in other neurological symptoms such as ataxia and dysphasia [133]. Long term observations over 2 years do not show significant improvements after 6 months. This points to the importance of stimulating therapies during the first 6 months, which should be followed by a strategy to help compensate for residual symptoms and signs.

A contrary development is observed in neurocognitive outcome. The earlier in life stroke happens, the worse the long-time problems are [134]. There is observed growing into deficits over the years. The deficits become more prominent with age – appropriate with higher demands on children [135]. Most affected areas are attention, short term memory, processing speed, visuospatial functions, and theory of mind [136–138]. Yet, despite persisting problems over the years quality of life of young adults after stroke is reported not to be affected [128]. In addition, there are no significant differences in long-term quality of life after stroke in children and young adults [127].

7.3. Post-stroke seizures and epilepsy

In general, paediatric patients experience seizures within the first day after stroke 18 times more frequently than adults [139]. Younger age and cortical ischaemia are risk factors for acute post-stroke seizures, defined as seizures occurring within the first week after stroke [140].

Post-stroke epilepsy is defined as two or more unprovoked seizures at any time between 48 h and two years after acute seizures [141]. Post-stroke epilepsy as well is reported to happen 4 times more frequently in children than in adults [142]. Importantly, seizures within the first 6 h after stroke are the most significant risk factor for post-stroke epilepsy [140]. The long-term follow-up of all patients with post-stroke epilepsy by a paediatric epileptologist is crucial.

In summary, the significant challenges following paediatric stroke underscore the importance of providing proper care for these patients. It is crucial to support them through their transition into adulthood and professional life.

Declaration of competing interest

The authors report no other financial disclosures relevant to the manuscript.

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References

[1] O. Eeg-Olofsson, Y. Ringheim, Stroke in children. Clinical characteristics and prognosis [Internet], Acta Paediatr. Scand. 72 (1983) 391–395. Available from: https://pubmed.ncbi.nlm.nih.gov/6880725/. (Accessed 3 April 2023).
[2] J. Broderick, T. Brott, E. Prenger, A. Leach, Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage [Internet], J. Child Neurol. 8 (1993) 250–255. Available from: https://pubmed.ncbi.nlm.nih.gov/8409267/. (Accessed 3 March 2023).
[3] M. Giroud, M. Lemesle, J.B. Gouyon, J.L. Nivelon, C. Milan, R. Dumas, Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993 [Internet], J. Clin. Epidemiol. 48 (1995) 1343–1348. Available from: https://pubmed.ncbi.nlm.nih.gov/7490597/. (Accessed 3 March 2023).
[4] C.J. Earley, S.J. Kittner, B.R. Feeser, J. Gardner, A. Epstein, M.A. Wozniak, R. Wityk, B.J. Stern, T.R. Price, R.F. Macko, et al., Stroke in children and sickle-cell disease [Internet], Neurology 51 (1998) 169–176. Available from: https://n.neurology.org/content/51/1/169. (Accessed 3 March 2023).
[5] D.B. Zahuranec, D.L. Brown, L.D. Lisabeth, L.B. Morgenstern, Is it time for a large, collaborative study of pediatric stroke? [Internet], Stroke 36 (2005) 1825–1829. Available from: https://pubmed.ncbi.nlm.nih.gov/16100029/. (Accessed 3 March 2023).
[6] M. Steinlin, I. Pfister, J. Pavlovic, R. Everts, E. Boltshauser, A.C. Mori, D. G. Mercati, C.A. Hänggeli, E. Keller, J. Luetschg, et al., The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors [Internet], Neuropediatrics 36 (2005) 90–97. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2005-837658. (Accessed 11 June 2019).
[7] B. Chung, V. Wong, Pediatric stroke among Hong Kong Chinese subjects [Internet], Pediatrics 114 (2004) e206–e212. Available from:/pediatrics/article/114/2/e206/64629/Pediatric-Stroke-Among-Hong-Kong-Chinese-Subjects. (Accessed 3 March 2023).
[8] A.A. Mallick, F.J. O'Callaghan, Prospective studies of the incidence of pediatric arterial ischaemic stroke, Blood Cells Mol. Dis. 69 (2018) 101.
[9] R.V. Krishnamurthi, T. Ikeda, V.L. Feigin, Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the global burden of disease study 2017, Neuroepidemiology 54 (2020) 171–179.
[10] H.J. Fullerton, Y.W. Wu, S. Zhao, S.C. Johnston, Risk of stroke in children: ethnic and gender disparities [Internet], Neurology 61 (2003) 189–194. Available from: https://pubmed.ncbi.nlm.nih.gov/12874397/. (Accessed 31 March 2023).
[11] M. Mastrangelo, L. Giordo, G. Ricciardi, M. De Michele, D. Toni, V. Leuzzi, Acute ischemic stroke in childhood: a comprehensive review [Internet], Eur. J. Pediatr. 181 (2022) 45–58. Available from: https://pubmed.ncbi.nlm.nih.gov/34327611/. (Accessed 1 April 2023).

[12] M.R. Golomb, H.J. Fullerton, U. Nowak-Gottl, G. Deveber, Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study [Internet], Stroke 40 (2009) 52–57. Available from: https://pubmed.ncbi.nlm.nih.gov/18787197/. (Accessed 31 March 2023).
[13] B. Balkaran, G. Char, J.S. Morris, P.W. Thomas, B.E. Serjeant, G.R. Serjeant, Stroke in a cohort of patients with homozygous sickle cell disease [Internet], J. Pediatr. 120 (1992) 360–366. Available from: https://pubmed.ncbi.nlm.nih.gov/1538280/. (Accessed 31 March 2023).
[14] F.J. Kirkham, I.A. Lagunju, Epidemiology of stroke in sickle cell disease [Internet], J. Clin. Med. 10 (2021). Available from: https://pubmed.ncbi.nlm.nih.gov/34575342/. (Accessed 31 March 2023).
[15] L.J. Marks, D. Munube, P. Kasirye, E. Mupere, Z. Jin, P. LaRussa, R. Idro, N. S. Green, Stroke prevalence in children with sickle cell disease in sub-saharan Africa: a systematic review and meta-analysis [Internet], Glob Pediatr Health 5 (2018). Available from: https://pubmed.ncbi.nlm.nih.gov/29785408/. (Accessed 31 March 2023).
[16] H.J. Fullerton, D.M. Chetkovich, Y.W. Wu, W.S. Smith, S.C. Johnston, Deaths from stroke in US children, 1979 to 1998 [Internet], Neurology 59 (2002) 34–39. Available from: https://pubmed.ncbi.nlm.nih.gov/12105304/. (Accessed 31 March 2023).
[17] H.J. Fullerton, J.S. Elkins, S.C. Johnston, Pediatric Stroke Belt: geographic variation in stroke mortality in US children [Internet], Stroke 35 (2004) 1570–1573. Available from: https://pubmed.ncbi.nlm.nih.gov/15178830/. (Accessed 31 March 2023).
[18] R. Riikonen, P. Santavuori, Hereditary and acquired risk factors for childhood stroke [Internet], Neuropediatrics 25 (1994) 227–233. Available from: https://pubmed.ncbi.nlm.nih.gov/7885530/. (Accessed 31 March 2023).
[19] C. Heller, S. Becker, W. Kreuz, I. Scharrer, Prothrombotic risk factors in childhood stroke and venous thrombosis [Internet], Eur. J. Pediatr. 158 (Suppl 3) (1999). Available from: https://pubmed.ncbi.nlm.nih.gov/10650849/. (Accessed 31 March 2023).
[20] V. Ganesan, M. Prengler, M.A. McShane, A.M. Wade, F.J. Kirkham, Investigation of risk factors in children with arterial ischemic stroke [Internet], Ann. Neurol. 53 (2003) 167–173. Available from: https://pubmed.ncbi.nlm.nih.gov/12557282/. (Accessed 31 March 2023).
[21] Y.Y. Lee, K.L. Lin, H.S. Wang, M.L. Chou, P.C. Hung, M.Y. Hsieh, J.J. Lin, A.M. C. Wong, Risk factors and outcomes of childhood ischemic stroke in Taiwan [Internet], Brain Dev. 30 (2008) 14–19. Available from: https://pubmed.ncbi.nlm.nih.gov/17573220/. (Accessed 31 March 2023).
[22] G. Kenet, L.K. Lütkhoff, M. Albisetti, T. Bernard, M. Bonduel, L. Brandao, S. Chabrier, A. Chan, G. Deveber, B. Fiedler, et al., Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies, Circulation 121 (2010) 1838–1847.
[23] M.T. MacKay, M. Wiznitzer, S.L. Benedict, K.J. Lee, G.A. Deveber, V. Ganesan, Arterial ischemic stroke risk factors: the international pediatric stroke study [Internet], Ann. Neurol. 69 (2011) 130–140. Available from: https://pubmed.ncbi.nlm.nih.gov/21280083/. (Accessed 31 March 2023).
[24] N.K. Hills, S.C. Johnston, S. Sidney, B.A. Zielinski, H.J. Fullerton, Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke [Internet], Ann. Neurol. 72 (2012) 850–858. Available from: https://pubmed.ncbi.nlm.nih.gov/23280836/. (Accessed 31 March 2023).
[25] A.A. Mallick, V. Ganesan, F.J. Kirkham, P. Fallon, T. Hedderly, T. McShane, A. P. Parker, E. Wassmer, E. Wraige, S. Amin, et al., Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study, Lancet Neurol. 13 (2014) 35–43.
[26] L. Gerstl, M.V. Bonfert, T. Nicolai, M. Dieterich, C. Adamczyk, F. Heinen, M. Olivieri, M. Steinlin, Childhood stroke: what are the special features of childhood stroke? Nervenarzt 88 (2017) 1367–1376.
[27] S.S. Rathore, A.R. Hinn, L.S. Cooper, H.A. Tyroler, W.D. Rosamond, Characterization of incident stroke signs and symptoms findings from the atherosclerosis risk in communities study, Stroke 33 (2002) 2718–2721.
[28] F.J. Liégeois, C. Mei, L. Pigdon, K.J. Lee, B. Stojanowski, M. Mackay, A. T. Morgan, Speech and language impairments after childhood arterial ischemic stroke: does hemisphere matter? [Internet], Pediatr. Neurol. 92 (2019) 55–59. Available from: https://pubmed.ncbi.nlm.nih.gov/30594525/. (Accessed 31 March 2023).
[29] R.K. Singh, N. Zecavati, J. Singh, H. Kaulas, K.B. Nelson, N.P. Dean, W. D. Gaillard, J. Carpenter, Seizures in acute childhood stroke, J. Pediatr. 160 (2012) 291–296.
[30] A. Yock-Corrales, M.T. MacKay, I. Mosley, W. Maixner, F.E. Babl, Acute childhood arterial ischemic and hemorrhagic stroke in the emergency department [Internet], Ann. Emerg. Med. 58 (2011) 156–163. Available from: https://pubmed.ncbi.nlm.nih.gov/21310508/. (Accessed 31 March 2023).
[31] R.N. Ichord, R. Bastian, L. Abraham, R. Askalan, S. Benedict, T.J. Bernard, L. Beslow, G. DeVeber, M. Dowling, N. Friedman, et al., Interrater reliability of the pediatric national institutes of health stroke scale (PedNIHSS) in a multicenter study, Stroke 42 (2011) 613–617.
[32] K.P.J. Braun, M.M.M. Bulder, S. Chabrier, F.J. Kirkham, C.S.P. Uiterwaal, M. Tardieu, G. Sébire, The course and outcome of unilateral intracranial arteriopathy in 79 children with ischaemic stroke [Internet], Brain 132 (2009) 544–557. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19039009. (Accessed 25 June 2019).
[33] K. Turkmen, I. Baloglu, Fabry disease: where are we now? Int. Urol. Nephrol. 52 (2020) 2113–2122.
[34] Y.Y. Wang, K.Y. Zhou, Y. Ye, F. Song, J. Yu, J.C. Chen, K. Yao, Moyamoya disease associated with morning glory disc anomaly and other ophthalmic findings: a mini-review, Front. Neurol. 11 (2020).
[35] I. Hori, T. Tsuji, M. Miyake, K. Ueda, E. Kataoka, M. Suzuki, S. Kobayashi, H. Kurahashi, Y. Takahashi, A. Okumura, et al., Delayed recognition of childhood arterial ischemic stroke, Pediatr. Int. 61 (2019) 895–903.
[36] M.T. Mackay, A. Yock-Corrales, L. Churilov, P. Monagle, G.A. Donnan, F.E. Babl, Differentiating childhood stroke from mimics in the emergency department, Stroke 47 (2016) 2476–2481.
[37] L.V. Gabis, R. Yangala, N.J. Lenn, Time lag to diagnosis of stroke in children, Available from: http://publications.aap.org/pediatrics/article-pdf/110/5/924/1116743/pe1102000924.pdf, 2002.
[38] M.F. Rafay, A.M. Pontigon, J. Chiang, M. Adams, D.A. Jarvis, F. Silver, D. MacGregor, G.A. Deveber, Delay to diagnosis in acute pediatric arterial ischemic stroke, Stroke 40 (2009) 58–64.
[39] S. Aroor, R. Singh, L.B. Goldstein, BE-FAST (balance, eyes, face, arm, speech, time): reducing the proportion of strokes missed using the FAST mnemonic [Internet], Stroke 48 (2017) 479–481. Available from: https://pubmed.ncbi.nlm.nih.gov/28082668/. (Accessed 6 December 2023).
[40] A. Khalaf, M. Iv, H. Fullerton, M. Wintermark, Pediatric stroke imaging, Pediatr. Neurol. 86 (2018) 5–18.
[41] H. Kamel, J.S. Healey, Cardioembolic stroke, Circ. Res. 120 (2017) 514–526.
[42] P.B. Sporns, H.J. Fullerton, S. Lee, H. Kim, W.D. Lo, M.T. Mackay, M. Wildgruber, Childhood stroke, Nat. Rev. Dis. Prim. 8 (2022).
[43] T.J. Bernard, M.J. Manco-Johnson, W. Lo, M.T. Mackay, V. Ganesan, N. A. Goldenberg, J. Armstrong-Wells, M.M. Dowling, E Steve Roach, M. Tripputi, et al., Towards a Consensus-Based Classification of Childhood Arterial Ischemic Stroke, 2011. Available from: http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.624585/-/DC1.
[44] H.J. Fullerton, M.K. Nancy Hills, M.S. Elkind, M.M. Michael Dowling, M. Wintermark, C.A. Glaser, M. Tan, M.J. Rivkin, L. Titomanlio, A. James Barkovich, et al., Infection, vaccination, and childhood arterial ischemic stroke Results of the VIPS study, Available from: http://data.worldbank.org/, 2015.
[45] M.S.V. Elkind, N.K. Hills, C.A. Glaser, W.D. Lo, C. Amlie-Lefond, N. Dlamini, R. Kneen, E.A. Hod, M. Wintermark, G.A. Deveber, et al., Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS study, Circulation 133 (2016) 732–741.
[46] M. Wintermark, N.K. Hills, G.A. DeVeber, A.J. Barkovich, M.S.V. Elkind, K. Sear, G. Zhu, C. Leiva-Salinas, Q. Hou, M.M. Dowling, et al., Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study [Internet], Stroke 45 (2014) 3597–3605. Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.114.007404. (Accessed 4 May 2019).
[47] M.T. Ziesmann, M. Nash, F.A. Booth, M.F. Rafay, Cardioembolic stroke in children: a clinical presentation and outcome study [Internet], Pediatr. Neurol. 51 (2014) 494–502. Available from: https://pubmed.ncbi.nlm.nih.gov/25266612/. (Accessed 6 December 2023).
[48] H. Asakai, M. Cardamone, D. Hutchinson, B. Stojanovski, J.C. Galati, M.M. H. Cheung, M.T. Mackay, Arterial Ischemic Stroke in Children with Cardiac Disease, 2015.
[49] B.C. Henzi, B. Brotschi, C. Balmer, B. Hennig, P. Rimensberger, M.H. Perez, J. P. Pfammatter, M. Beghetti, N. Sekarski, A.N. Datta, et al., Risk factors for postprocedural arterial ischemic stroke in children with cardiac disease, Stroke (2020) 242–245.
[50] C.D. Fraser, R.D.B. Jaquiss, D.N. Rosenthal, T. Humpl, C.E. Canter, E. H. Blackstone, D.C. Naftel, R.N. Ichord, L. Bomgaars, J.S. Tweddell, et al., Prospective trial of a pediatric ventricular assist device, N. Engl. J. Med. 367 (2012) 532–541.
[51] L.C. Jordan, R.N. Ichord, O. Reinhartz, T. Humpl, S. Pruthi, C. Tjossem, D. N. Rosenthal, Neurological complications and outcomes in the berlin heart EXCOR® pediatric investigational device exemption trial, J. Am. Heart Assoc. 4 (2015).
[52] M.T. MacKay, S.P. Prabhu, L. Coleman, Childhood posterior circulation arterial ischemic stroke [Internet], Stroke 41 (2010) 2201–2209. Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.110.583831. (Accessed 9 July 2019).
[53] M.F. Rafay, K.A. Shapiro, A.M. Surmava, G.A. deVeber, A. Kirton, H.J. Fullerton, C. Amlie-Lefond, B. Weschke, N. Dlamini, J.L. Carpenter, et al., Spectrum of cerebral arteriopathies in children with arterial ischemic stroke [Internet], Neurology 94 (2020) e2479–e2490. Available from: https://pubmed.ncbi.nlm.nih.gov/32457211/. (Accessed 7 November 2020).
[54] M. Wintermark, N.K. Hills, G.A. De Veber, A.J. Barkovich, T.J. Bernard, N. R. Friedman, M.T. Mackay, A. Kirton, G. Zhu, C. Leiva-Salinas, et al., Clinical and imaging characteristics of arteriopathy subtypes in children with arterial ischemic stroke: results of the vips study [Internet], Am. J. Neuroradiol. 38 (2017) 2172–2179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5985237/. (Accessed 21 June 2019).
[55] M. Fink, N. Slavova, S. Grunt, E. Perret, M. Regényi, M. Steinlin, S. Bigi, Posterior arterial ischemic stroke in childhood: clinical features and neuroimaging characteristics, Stroke 50 (2019) 2329–2335.
[56] R. Sträter, S. Becker, A. Von Eckardstein, A. Heinecke, S. Gutsche, R. Junker, K. Kurnik, R. Schobess, U. Nowak-Göttl, Prospective assessment of risk factors for recurrent stroke during childhood–a 5-year follow-up study [Internet], Lancet 360 (2002) 1540–1545. Available from: https://pubmed.ncbi.nlm.nih.gov/12443591/. (Accessed 31 March 2023).

[57] C. Grose, A. Shaban, H.J. Fullerton, Common features between stroke following Varicella in children and stroke following herpes zoster in adults: varicella-zoster virus in trigeminal ganglion, in: Current Topics in Microbiology and Immunology, Springer Science and Business Media Deutschland GmbH, 2023, pp. 247–272.
[58] J.E. Lin, A. Asfour, T.B. Sewell, B. Hooe, P. Pryce, C. Earley, M.Y. Shen, M. Kerner-Rossi, K.T. Thakur, W.S. Vargas, et al., Neurological issues in children with COVID-19, Neurosci. Lett. 743 (2021).
[59] M.C. Cornet, C. Grose, Z. Vexler, Y.W. Wu, H.J. Fullerton, The role of infection and inflammation in the pathogenesis of pediatric arterial ischemic stroke, Semin. Pediatr. Neurol. 44 (2022).
[60] S.K. Nanda, S. Jayalakshmi, S. Mohandas, Pediatric ischemic stroke due to dengue vasculitis, Pediatr. Neurol. 51 (2014) 570–572.
[61] O. Monteventi, M. Steinlin, M. Regényi, E. Roulet-Perez, P. Weber, J. Fluss, Pediatric stroke related to lyme neuroborreliosis: data from the Swiss NeuroPaediatric stroke Registry and literature review, Eur. J. Paediatr. Neurol. 22 (2018) 113–121.
[62] F.A. Perez, G. Oesch, C.M. Amlie-Lefond, MRI vessel wall enhancement and other imaging biomarkers in pediatric focal cerebral arteriopathy-inflammatory subtype, Stroke (2020) 853–859.
[63] N.V. Stence, L.L. Pabst, A.L. Hollatz, D.M. Mirsky, P.S. Herson, S. Poisson, R. J. Traystman, T.J. Bernard, Predicting progression of intracranial arteriopathies in childhood stroke with vessel wall imaging, Stroke 48 (2017) 2274–2277.
[64] H.J. Fullerton, N. Stence, N.K. Hills, B. Jiang, C. Amlie-Lefond, T.J. Bernard, N. R. Friedman, R. Ichord, M.T. Mackay, M.F. Rafay, et al., Focal cerebral arteriopathy of childhood [Internet], Stroke 49 (2018) 2590–2596. Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.118.021556. (Accessed 4 May 2019).
[65] H.J. Fullerton, S Claiborne Johnston, W.S. Smith, Arterial Dissection and Stroke in Children, Available from:, 2001 www.neurology.org.
[66] H. Oshima, Y. Katayama, Discovery of cerebrovascular moyamoya disease: research during the late 1950s and early 1960s, Child's Nerv. Syst. 28 (2012) 497–500.
[67] R.M. Scott, E.R. Smith, Moyamoya Disease and Moyamoya Syndrome, 2009.
[68] C. Asselman, D. Hemelsoet, D. Eggermont, B. Dermaut, F. Impens, Moyamoya disease emerging as an immune-related angiopathy, Trends Mol. Med. 28 (2022) 939–950.
[69] D. Zhang, L. Huang, Z. Huang, Q. Zhou, X. Yang, H. Gu, Z. Li, Y. Shi, L. Gan, H. Wang, et al., Epidemiology of Moyamoya disease in China: a nationwide hospital-based study [Internet], Lancet Reg Health West Pac 18 (2021). Available from: https://pubmed.ncbi.nlm.nih.gov/35024660/. (Accessed 1 April 2023).
[70] M. Ihara, Y. Yamamoto, Y. Hattori, W. Liu, H. Kobayashi, H. Ishiyama, T. Yoshimoto, S. Miyawaki, T. Clausen, O.Y. Bang, et al., Moyamoya disease: diagnosis and interventions, Lancet Neurol. 21 (2022) 747–758.
[71] D. Houzelstein, D. Simon-Chazottes, L. Batista, S. Tokuda, F. Langa Vives, M. Flamand, X. Montagutelli, J.J. Panthier, The ring finger protein 213 gene (Rnf213) contributes to Rift Valley fever resistance in mice [Internet], Mamm. Genome 32 (2021) 30–37. Available from: https://pubmed.ncbi.nlm.nih.gov/33420513/. (Accessed 1 April 2023).
[72] N. Khan, B. Schuknecht, E. Boltshauser, A. Capone, A. Buck, H.G. Imhof, Y. Yonekawa, Moyamoya disease and Moyamoya syndrome: experience in Europe; choice of revascularisation procedures, Acta Neurochir. 145 (2003) 1061–1071.
[73] D.M. Milewicz, C.S. Kwartler, C.L. Papke, E.S. Regalado, J. Cao, A.J. Reid, Genetic variants promoting smooth muscle cell proliferation can result in diffuse and diverse vascular diseases: evidence for a hyperplastic vasculomyopathy, Genet. Med. 12 (2010) 196–203.
[74] L.M. van den Bersselaar, J.M.A. Verhagen, J.A. Bekkers, M. Kempers, A. C. Houweling, M. Baars, E. Overwater, Y. Hilhorst-Hofstee, D.Q.C.M. Barge-Schaapveld, E. Rompen, et al., Expanding the genetic and phenotypic spectrum of ACTA2-related vasculopathies in a Dutch cohort, Genet. Med. (2022).
[75] N. McCrea, H.J. Fullerton, V. Ganesan, Genetic and environmental associations with pediatric cerebral arteriopathy: insights into disease mechanisms, Stroke 50 (2019) 257–265.
[76] Q. Zhou, D. Yang, A.K. Ombrello, A.V. Zavialov, C. Toro, A.V. Zavialov, D. L. Stone, J.J. Chae, S.D. Rosenzweig, K. Bishop, et al., Early-onset stroke and vasculopathy associated with mutations in ADA2, N. Engl. J. Med. 370 (2014) 911–920.
[77] A. Bersano, M. Kraemer, A. Burlina, M. Mancuso, J. Finsterer, S. Sacco, C. Salvarani, L. Caputi, H. Chabriat, S.L. Oberstein, et al., Heritable and non-heritable uncommon causes of stroke, J. Neurol. 268 (2021) 2780–2807.
[78] S. Tikka, M. Baumann, M. Siitonen, P. Pasanen, M. Pöyhönen, L. Myllykangas, M. Viitanen, T. Fukutake, E. Cognat, A. Joutel, et al., CADASIL and CARASIL, Brain Pathol. 24 (2014) 525–544.
[79] D. Rea, J.F. Brandsema, D. Armstrong, P.C. Parkin, G. DeVeber, D. MacGregor, W. J. Logan, R. Askalan, Cerebral arteriopathy in children with neurofibromatosis type 1 [Internet], Pediatrics 124 (2009). Available from: https://pubmed.ncbi.nlm.nih.gov/19706560/. (Accessed 1 April 2023).
[80] K.M. Emerick, I.D. Krantz, B.M. Kamath, C. Darling, D.M. Burrowes, N.B. Spinner, P.F. Whitington, D.A. Piccoli, Intracranial vascular abnormalities in patients with Alagille syndrome [Internet], J. Pediatr. Gastroenterol. Nutr. 41 (2005) 99–107. Available from: https://journals.lww.com/jpgn/Fulltext/2005/07000/Intracranial_Vascular_Abnormalities_in_Patients.19.aspx. (Accessed 1 April 2023).
[81] I. Volonghi, M. Frigerio, D. Mardighian, R. Gasparotti, E. Del Zotto, A. Giossi, P. Costa, L. Poli, G. Jeannin, G.A. Gregorini, et al., Grange syndrome: an identifiable cause of stroke in young adults [Internet], Am. J. Med. Genet. 158A (2012) 2894–2898. Available from: https://pubmed.ncbi.nlm.nih.gov/22987684/. (Accessed 1 April 2023).
[82] S.Y. Kuang, Y. Li, S.L. Yang, X. Han, Child neurology: aicardi-goutières syndrome presenting as recurrent ischemic stroke, Neurology 99 (2022) 393–398.
[83] B.S. Joly, P. Coppo, A. Veyradier, Pediatric thrombotic thrombocytopenic purpura, Eur. J. Haematol. 101 (2018) 425–434.
[84] D.M. Ferriero, H.J. Fullerton, T.J. Bernard, L. Billinghurst, S.R. Daniels, M. R. Debaun, G. Deveber, R.N. Ichord, L.C. Jordan, P. Massicotte, et al., Management of stroke in neonates and children: a scientific statement from the American Heart Association/American stroke association, Stroke 50 (2019) E51–E96.
[85] J. Klučka, E. Klabusayová, T. Musilová, T. Kramplová, T. Skřívšovská, M. Kratochvíl, M. Kosinová, O. Horák, H. Ošlejšková, P. Jabandžiev, et al., Pediatric patient with ischemic stroke: initial approach and early management [Internet], Children 8 (2021). Available from: https://pubmed.ncbi.nlm.nih.gov/34438540/. (Accessed 1 April 2023).
[86] C.A. Rawanduzy, E. Earl, G. Mayer, B. Lucke-Wold, Pediatric stroke: a review of common etiologies and management strategies [Internet], Biomedicines 11 (2022). Available from: https://pubmed.ncbi.nlm.nih.gov/36672510/. (Accessed 2 April 2023).
[87] E.F.M. Wijdicks, K.N. Sheth, B.S. Carter, D.M. Greer, S.E. Kasner, W.T. Kimberly, S. Schwab, E.E. Smith, R.J. Tamargo, M. Wintermark, Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association [Internet], Stroke 45 (2014) 1222–1238. Available from: https://pubmed.ncbi.nlm.nih.gov/24481970/. (Accessed 6 December 2023).
[88] P.M. Kochanek, R.C. Tasker, N. Carney, A.M. Totten, P.D. Adelson, N.R. Selden, C. Davis-O'Reilly, E.L. Hart, M.J. Bell, S.L. Bratton, et al., Guidelines for the management of pediatric severe traumatic brain injury, third edition: update of the brain trauma foundation guidelines, executive summary [Internet], Neurosurgery 84 (2019) 1169–1178. Available from: https://pubmed.ncbi.nlm.nih.gov/30822776/. (Accessed 3 April 2023).
[89] N.S. Abend, L.A. Beslow, S.E. Smith, S.K. Kessler, A. Vossough, S. Mason, S. Agner, D.J. Licht, R.N. Ichord, Seizures as a presenting symptom of acute arterial ischemic stroke in childhood [Internet], J. Pediatr. 159 (2011) 479–483. Available from: https://pubmed.ncbi.nlm.nih.gov/21429519/. (Accessed 2 April 2023).
[90] M.J. Rivkin, G. De Veber, R.N. Ichord, A. Kirton, A.K. Chan, C.A. Hovinga, J. C. Gill, A. Szabo, M.D. Hill, K. Scholz, et al., Thrombolysis in pediatric stroke study [Internet], Stroke 46 (2015) 880–885. Available from: https://pubmed.ncbi.nlm.nih.gov/25613306/. (Accessed 1 April 2023).
[91] C. Amlie-Lefond, G. deVeber, A.K. Chan, S. Benedict, T. Bernard, J. Carpenter, M. M. Dowling, H. Fullerton, C. Hovinga, A. Kirton, et al., Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study [Internet], Lancet Neurol. 8 (2009) 530–536. Available from: https://pubmed.ncbi.nlm.nih.gov/19423401/. (Accessed 1 April 2023).
[92] T.J. Bernard, M.J. Rivkin, K. Scholz, G. De Veber, A. Kirton, J.C. Gill, A.K. Chan, C.A. Hovinga, R.N. Ichord, J.C. Grotta, et al., Emergence of the primary pediatric stroke center: impact of the thrombolysis in pediatric stroke trial [Internet], Stroke 45 (2014) 2018–2023. Available from: https://pubmed.ncbi.nlm.nih.gov/24916908/. (Accessed 1 April 2023).
[93] T.R. Ladner, J. Mahdi, M.C. Gindville, A. Gordon, ZL eah Harris, K. Crossman, S. Pruthi, T.J. Abramo, L.C. Jordan, Pediatric acute stroke protocol activation in a children's hospital emergency department [Internet], Stroke 46 (2015) 2328–2331. Available from: https://pubmed.ncbi.nlm.nih.gov/26138119/. (Accessed 1 April 2023).
[94] D.C. Lauzier, M.M. Galardi, K.P. Guilliams, M.S. Goyal, C. Amlie-Lefond, D. K. Hallam, A.P. Kansagra, Pediatric thrombectomy: design and workflow lessons from two experienced centers [Internet], Stroke 52 (2021) 1511–1519. Available from: https://pubmed.ncbi.nlm.nih.gov/33691502/. (Accessed 1 April 2023).
[95] S. Bigi, A. Dulcey, J. Gralla, C. Bernasconi, A. Melliger, A.N. Datta, M. Arnold, J. Kaesmacher, J. Fluss, A. Hackenberg, et al., Feasibility, safety, and outcome of recanalization treatment in childhood stroke, Ann. Neurol. 83 (2018) 1125–1132.
[96] I. Fragata, T. Morais, R. Silva, A.P. Nunes, P. Loureiro, J. Diogo Martins, J. Pamplona, R. Carvalho, M. Baptista, J. Reis, Endovascular treatment of pediatric ischemic stroke: a single center experience and review of the literature [Internet], Intervent Neuroradiol. 27 (2021) 16–24. Available from: https://pubmed.ncbi.nlm.nih.gov/32903115/. (Accessed 1 April 2023).
[97] P.B. Sporns, A. Kemmling, U. Hanning, J. Minnerup, R. Sträter, T. Niederstadt, W. Heindel, M. Wildgruber, Thrombectomy in childhood stroke [Internet], J. Am. Heart Assoc. 8 (2019). Available from: https://pubmed.ncbi.nlm.nih.gov/30803281/. (Accessed 1 April 2023).
[98] T. Rambaud, N. Legris, Y. Bejot, C. Bellesme, B. Lapergue, E. Jouvent, F. Pico, D. Smadja, M. Zuber, S. Crozier, et al., Acute ischemic stroke in adolescents [Internet], Neurology 94 (2020) E158–E169. Available from: https://pubmed.ncbi.nlm.nih.gov/31831601/. (Accessed 2 April 2023).
[99] M. Kossorotoff, B. Kerleroux, G. Boulouis, B. Husson, K. Tran Dong, F. Eugene, L. Damaj, A. Ozanne, C. Bellesme, A. Rolland, et al., Recanalization treatments for pediatric acute ischemic stroke in France [Internet], JAMA Netw. Open 5 (2022). Available from: https://pubmed.ncbi.nlm.nih.gov/36107427/. (Accessed 2 April 2023).
[100] C. Amlie-Lefond, D.W.W. Shaw, A. Cooper, M.S. Wainwright, A. Kirton, R. J. Felling, M.G. Abraham, M.T. MacKay, M.M. Dowling, M. Torres, et al., Risk of intracranial hemorrhage following intravenous tPA (Tissue-Type plasminogen activator) for acute stroke is low in children [Internet], Stroke 51 (2020)

542–548. Available from: https://pubmed.ncbi.nlm.nih.gov/31842706/. (Accessed 3 April 2023).
[101] K.P. Vinayan, V. Nambiar, V. Anand, Acute ischemic stroke in children - should we thrombolyze? [Internet], Ann. Indian Acad. Neurol. 25 (2022) 21–25. Available from: https://pubmed.ncbi.nlm.nih.gov/35342261/. (Accessed 1 April 2023).
[102] P.B. Sporns, R. Sträter, J. Minnerup, H. Wiendl, U. Hanning, R. Chapot, H. Henkes, E. Henkes, A. Grams, F. Dorn, et al., Feasibility, safety, and outcome of endovascular recanalization in childhood stroke: the save ChildS study [Internet], JAMA Neurol. 77 (2020) 25–34. Available from: https://pubmed.ncbi.nlm.nih.gov/31609380/. (Accessed 1 April 2023).
[103] P.B. Sporns, M.N. Psychogios, R. Straeter, U. Hanning, J. Minnerup, R. Chapot, H. Henkes, E. Henkes, A. Grams, F. Dorn, et al., Clinical diffusion mismatch to select pediatric patients for embolectomy 6 to 24 hours after stroke: an analysis of the save ChildS study [Internet], Neurology 96 (2021) E343–E351. Available from: https://pubmed.ncbi.nlm.nih.gov/33144517/. (Accessed 2 April 2023).
[104] C. Bilgin, M. Ibrahim, A.Y. Azzam, S. Ghozy, A. Elswedy, H. Kobeissi, M. Sobhi Jabal, R. Kadirvel, G. Boulouis, O. Naggara, et al., Mechanical thrombectomy for pediatric large vessel occlusions : a systematic review and meta-analysis [Internet], Clin. Neuroradiol. (2023). Available from: https://pubmed.ncbi.nlm.nih.gov/36592199/. (Accessed 2 April 2023).
[105] S. Lee, B. Jiang, M. Wintermark, M. Mlynash, S. Christensen, R. Sträter, G. Broocks, A. Grams, F. Dorn, O. Nikoubashman, et al., Cerebrovascular collateral integrity in pediatric large vessel occlusion: analysis of the save ChildS study [Internet], Neurology 98 (2021) E352–E363. Available from: https://pubmed.ncbi.nlm.nih.gov/34795051/. (Accessed 2 April 2023).
[106] P.B. Sporns, A. Kemmling, S. Lee, H. Fullerton, W.G. Kunz, J.L. Wilson, M. T. Mackay, M. Steinlin, J. Fiehler, M. Psychogios, et al., A prospective multicenter Registry on feasibility, safety, and outcome of endovascular recanalization in childhood stroke (save ChildS pro) [Internet], Front. Neurol. 12 (2021). Available from: https://pubmed.ncbi.nlm.nih.gov/34539563/. (Accessed 1 April 2023).
[107] W.G. Kunz, P.B. Sporns, M.N. Psychogios, J. Fiehler, R. Chapot, F. Dorn, A. Grams, A. Morotti, P. Musolino, S. Lee, et al., Cost-effectiveness of endovascular thrombectomy in childhood stroke: an analysis of the save ChildS study [Internet], J Stroke 24 (2022) 138–147. Available from: https://pubmed.ncbi.nlm.nih.gov/35135067/. (Accessed 1 April 2023).
[108] T.L. Medley, C. Miteff, I. Andrews, T. Ware, M. Cheung, P. Monagle, S. Mandelstam, A. Wray, C. Pridmore, C. Troedson, et al., Australian Clinical Consensus Guideline: the diagnosis and acute management of childhood stroke [Internet], Int. J. Stroke 14 (2019) 94–106. Available from: https://pubmed.ncbi.nlm.nih.gov/30284961/. (Accessed 3 April 2023).
[109] N.A. Goldenberg, T.J. Bernard, H.J. Fullerton, A. Gordon, G. deVeber, Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischaemic stroke: a multicentre, observational, cohort study [Internet], Lancet Neurol. 8 (2009) 1120–1127. Available from: https://pubmed.ncbi.nlm.nih.gov/19801204/. (Accessed 3 April 2023).
[110] P. Monagle, Congenital heart disease and thrombosis: what do we know?, 2014 11:3 [Internet], Nat. Rev. Cardiol. 11 (2014) 132–134. Available from: https://www.nature.com/articles/nrcardio.2013.217. (Accessed 3 April 2023).
[111] H.S. Markus, C. Levi, A. King, J. Madigan, J. Norris, Antiplatelet therapy vs anticoagulation therapy in cervical artery dissection: the cervical artery dissection in stroke study (CADISS) randomized clinical trial final results [Internet], JAMA Neurol. 76 (2019) 657–664. Available from: https://pubmed.ncbi.nlm.nih.gov/30801621/. (Accessed 3 April 2023).
[112] M. Steinlin, S. Bigi, B. Stojanovski, J. Gajera, M. Regényi, M. El-Koussy, M. T. MacKay, Focal cerebral arteriopathy: do Steroids improve outcome? Stroke 48 (2017) 2375–2382.
[113] D. Brechbühl, L. Steiner, R. Münger, G. Oesch-Nementh, E.I. Piechowiak, P. Massatsch, M. Branca, M. Sauermann, A.N. Datta, J. Fluss, et al., High dose Steroids in children with stroke and unilateral focal arteriopathy: a multicentre randomized controlled trial PASTA (paediatric arteriopathy steroid aspirin) trial study protocol, Pediatr Stroke (2022).
[114] Y. Park, H.J. Fullerton, J.J. Elm, A pragmatic, adaptive clinical trial design for a rare disease: the FOcal Cerebral Arteriopathy Steroid (FOCAS) trial [Internet], Contemp. Clin. Trials 86 (2019). Available from: https://pubmed.ncbi.nlm.nih.gov/31614215/. (Accessed 3 April 2023).
[115] A.J. Giustini, S.A. Stone, C. Ramamoorthy, Moyamoya disease in children and its anesthetic implications: a review [Internet], Paediatr. Anaesth. 30 (2020) 1191–1198. Available from: https://pubmed.ncbi.nlm.nih.gov/33463884/. (Accessed 3 April 2023).
[116] S. Guey, E. Tournier-Lasserve, D. Hervé, M. Kossorotoff, Moyamoya disease and syndromes: from genetics to clinical management [Internet], Appl. Clin. Genet. 8 (2015) 49–68. Available from: https://pubmed.ncbi.nlm.nih.gov/25733922/. (Accessed 3 April 2023).
[117] R. Guzman, M. Lee, A. Achrol, T. Bell-Stephens, M. Kelly, H.M. Do, M.P. Marks, G. K. Steinberg, Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article [Internet], J. Neurosurg. 111 (2009) 927–935. Available from: https://pubmed.ncbi.nlm.nih.gov/19463046/. (Accessed 3 April 2023).
[118] E.R. Smith, R.M. Scott, Spontaneous occlusion of the circle of Willis in children: pediatric moyamoya summary with proposed evidence-based practice guidelines. A review [Internet], J. Neurosurg. Pediatr. 9 (2012) 353–360. Available from: https://pubmed.ncbi.nlm.nih.gov/22462697/. (Accessed 3 April 2023).
[119] R. Appireddy, M. Ranjan, B.A. Durafourt, J. Riva-Cambrin, W.J. Hader, P. D. Adelson, Surgery for moyamoya disease in children [Internet], J. Child Neurol. 34 (2019) 517–529. Available from: https://pubmed.ncbi.nlm.nih.gov/31066331/. (Accessed 3 April 2023).
[120] L.J. Estcourt, R. Kohli, S. Hopewell, M. Trivella, W.C. Wang, Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease [Internet], Cochrane Database Syst. Rev. 7 (2020). Available from: https://pubmed.ncbi.nlm.nih.gov/32716555/. (Accessed 3 April 2023).
[121] M.R. DeBaun, L.C. Jordan, A.A. King, J. Schatz, E. Vichinsky, C.K. Fox, R. C. McKinstry, P. Telfer, M.A. Kraut, L. Daraz, et al., American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults [Internet], Blood Adv 4 (2020) 1554–1588, https://doi.org/10.1182/bloodadvances.2019001142. (Accessed 6 December 2023).
[122] T. Aprasidze, T. Shatirishvili, G. Oesch, G. Lomidze, N. Tatishvili, Outcome in childhood stroke: comparing functional outcome by modified Rankin scale with neurological outcome by pediatric stroke outcome measure, J. Pediatr. Neurol. (2023).
[123] D. Hebert, M.P. Lindsay, A. McIntyre, A. Kirton, P.G. Rumney, S. Bagg, M. Bayley, D. Dowlatshahi, S. Dukelow, M. Garnhum, et al., Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015 [Internet], Int. J. Stroke 11 (2016) 459–484. Available from: https://pubmed.ncbi.nlm.nih.gov/27079654/. (Accessed 3 April 2023).
[124] F.Y. Ismail, A. Fatemi, M.V. Johnston, Cerebral plasticity: windows of opportunity in the developing brain [Internet], Eur. J. Paediatr. Neurol. 21 (2017) 23–48. Available from: http://www.ejpn-journal.com/article/S1090379816300964/fulltext. (Accessed 3 April 2023).
[125] R. Everts, J. Pavlovic, F. Kaufmann, B. Uhlenberg, U. Seidel, K. Nedeltchev, W. Perrig, M. Steinlin, Cognitive functioning, behavior, and quality of life after stroke in childhood, 14:323–338. Available from: https://www.tandfonline.com/doi/abs/10.1080/09297040701792383, 2008. (Accessed 3 April 2023).
[126] L. Steiner, A. Federspiel, J. Jaros, N. Slavova, R. Wiest, M. Steinlin, S. Grunt, R. Everts, Cerebral blood flow and cognitive outcome after pediatric stroke in the middle cerebral artery [Internet], Sci. Rep. 11 (2021). Available from: https://pubmed.ncbi.nlm.nih.gov/34593847/. (Accessed 3 April 2023).
[127] B.G. Simonetti, A. Cavelti, M. Arnold, S. Bigi, M. Regényi, H.P. Mattle, J. Gralla, J. Fluss, P. Weber, A. Hackenberg, et al., Long-term Outcome after Arterial Ischemic Stroke in Children and Young Adults, 2015.
[128] S. Bigi, U. Fischer, E. Wehrli, H.P. Mattle, E. Boltshauser, S. Bürki, P.Y. Jeannet, J. Fluss, P. Weber, K. Nedeltchev, et al., Acute ischemic stroke in children versus young adults [Internet], Ann. Neurol. 70 (2011) 245–254. Available from: https://pubmed.ncbi.nlm.nih.gov/21823153/. (Accessed 3 April 2023).
[129] A.A. Mallick, V. Ganesan, F.J.K. O'Callaghan, Mortality from childhood stroke in England and Wales, 1921-2000 [Internet], Arch. Dis. Child. 95 (2010) 12–19. Available from: https://pubmed.ncbi.nlm.nih.gov/19951935/. (Accessed 3 April 2023).
[130] K.D. Statler, L. Dong, D.M. Nielsen, S.L. Bratton, Pediatric stroke: clinical characteristics, acute care utilization patterns, and mortality [Internet], Childs Nerv Syst 27 (2011) 565–573. Available from: https://pubmed.ncbi.nlm.nih.gov/20922396/. (Accessed 3 April 2023).
[131] C.K. Fox, N.K. Hills, D.R. Vinson, A.L. Numis, R.A. Dicker, S. Sidney, H. J. Fullerton, Population-based study of ischemic stroke risk after trauma in children and young adults [Internet], Neurology 89 (2017) 2310–2316. Available from: https://pubmed.ncbi.nlm.nih.gov/29117963/. (Accessed 31 March 2023).
[132] R.V. Krishnamurthi, G. Deveber, V.L. Feigin, S. Barker-Collo, H. Fullerton, M. T. Mackay, F. O'Callahan, M.P. Lindsay, A. Kolk, W. Lo, et al., Stroke prevalence, mortality and disability-adjusted life years in children and youth aged 0-19 Years: data from the global and regional burden of stroke 2013 [Internet], Neuroepidemiology 45 (2015) 177–189. Available from: https://pubmed.ncbi.nlm.nih.gov/26505982/. (Accessed 3 April 2023).
[133] J. Pavlovic, F. Kaufmann, E. Boltshauser, A. Capone Mori, D. Gubser Mercati, C. A. Haenggeli, E. Keller, J. Lütschg, J.P. Marcoz, G.P. Ramelli, et al., Neuropsychological problems after paediatric stroke: two year follow-up of Swiss children [Internet], Neuropediatrics 37 (2006) 13–19. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2006-923932. (Accessed 12 June 2019).
[134] M. Studer, E. Boltshauser, A. Capone Mori, A. Datta, J. Fluss, D. Mercati, A. Hackenberg, E. Keller, O. Maier, J.-P. Marcoz, et al., Factors affecting cognitive outcome in early pediatric stroke [Internet], Neurology 82 (2014) 784–792. Available from: http://www.neurology.org/cgi/doi/10.1212/WNL.0000000000000162. (Accessed 13 September 2019).
[135] A. Fuentes, A. Deotto, M. Desrocher, G. DeVeber, R. Westmacott, Determinants of cognitive outcomes of perinatal and childhood stroke: a review [Internet], Child Neuropsychol. 22 (2016) 1–38. Available from: https://pubmed.ncbi.nlm.nih.gov/25355013/. (Accessed 4 April 2023).
[136] R. Everts, J. Pavlovic, F. Kaufmann, B. Uhlenberg, U. Seidel, K. Nedeltchev, W. Perrig, M. Steinlin, Cognitive functioning, behavior, and quality of life after stroke in childhood, 14:323–338. Available from: https://www.tandfonline.com/doi/abs/10.1080/09297040701792383, 2008. (Accessed 3 April 2023).
[137] W. Lo, X. Li, K. Hoskinson, K. McNally, M. Chung, J.E. Lee, J. Wang, Z.L. Lu, K. Yeates, Pediatric stroke impairs theory of mind performance [Internet], J. Child Neurol. 35 (2020) 228–234. Available from: https://pubmed.ncbi.nlm.nih.gov/31775563/. (Accessed 4 April 2023).
[138] C.A. Hajek, K.O. Yeates, V. Anderson, M. Mackay, M. Greenham, A. Gomes, W. Lo, Cognitive outcomes following arterial ischemic stroke in infants and children [Internet], J. Child Neurol. 29 (2014) 887–894. Available from: https://pubmed.ncbi.nlm.nih.gov/23760990/. (Accessed 4 April 2023).

[139] N.M.M. Morais, J. Ranzan, R.S. Riesgo, Predictors of epilepsy in children with cerebrovascular disease [Internet], J. Child Neurol. 28 (2013) 1387–1391. Available from: https://pubmed.ncbi.nlm.nih.gov/23143721/. (Accessed 6 December 2023).

[140] İ. Polat, U. Yiş, M. Ayanoğlu, D. Okur, P. Edem, C. Paketçi, E. Bayram, S. Hız Kurul, Risk factors of post-stroke epilepsy in children; experience from a tertiary center and a brief review of the literature [Internet], J. Stroke Cerebrovasc. Dis. 30 (2021). Available from: https://pubmed.ncbi.nlm.nih.gov/33197802/. (Accessed 6 December 2023).

[141] I. Breitweg, C von Stülpnagel, T. Pieper, K. Lidzba, H. Holthausen, M. Staudt, G. Kluger, Early seizures predict the development of epilepsy in children and adolescents with stroke [Internet], Eur. J. Paediatr. Neurol. 21 (2017) 465–467. Available from: https://pubmed.ncbi.nlm.nih.gov/28041798/. (Accessed 6 December 2023).

[142] C.K. Fox, H.C. Glass, S. Sidney, D.H. Lowenstein, H.J. Fullerton, Acute seizures predict epilepsy after childhood stroke [Internet], Ann. Neurol. 74 (2013) 249–256. Available from: https://pubmed.ncbi.nlm.nih.gov/23613472/. (Accessed 6 December 2023).