A Clinical Approach to Arterial Ischemic Childhood Stroke: Increasing Knowledge over the Last Decade

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Abstract

Childhood stroke is increasingly being recognized as an important burden not only for affected children and families, but also for socioeconomic reasons. A primary problem is delayed diagnosis, due to the many mimics of childhood stroke, and the variety of manifesting symptoms. The most important is hemiparesis (with/without dysphasia or facial palsy), but ataxia, seizures, and many more are also possible. Suspicions of stroke has to be ascertained by neuroimaging, gold standard being (diffusion weighted) magnetic resonance. Risk factors are multiple, but their presence might help to increase the suspicion of stroke. The most important factors are infectious/parainfectious etiologies, frequently possibly manifesting by transient focal cerebral arteriopathy (FCA). Cardiological underlying problems are the second most important. Arterio-pathies can be detected in about half of the children, besides FCA and dissection and MoyaMoya disease are the most important. Hereditary coagulopathies increase the risk of stroke. There is still a controversy on best treatment in children: platelet antiaggregation and heparinization are used about equally. Thrombolysis is being discussed increasingly. Severity of symptoms at manifestation and on follow-up are not less significant in children than in young adults. About two-third of the children have significant residual neurological problems and a majority cognitive and behavior problems.

Keywords

► childhood stroke
► risk factors
► etiology
► treatment
► manifestation
► outcome

Stroke is a rare, but terrifying and devastating disease in childhood. Over the last two decades, childhood stroke is increasingly being recognized as an important cause of childhood morbidity and ranges among the top 10 causes of death in children.1–3 Thus childhood stroke is an important burden, not only for affected children and their families, but also for health insurances and socioeconomic reasons. The costs for pediatric stroke are substantial: In an North American study, the average cost of a childhood stroke admission was $81,869, the average adjusted 5 years costs are $135,161.4 International data suggest an incidence of childhood stroke of ~2 to 5/100,000 children per year.5 Data from the Swiss Neuropediatric Stroke Registry suggest an incidence for arterial ischemic stroke (AIS) in childhood of 2.1/100,000 children per year.5 There is a suggestion of a higher incidence, due to clinically unrecognized events.6 For yet unknown reasons there is a worldwide male predominance in childhood stroke.7,8

Many excellent reviews have been published recently.1,9–12 There are three guidelines for treatment published.13–15 This article will not attempt to give a review of the subject, but will try to guide a physician through many aspects one has to consider, dealing with a child with acute arterial ischemic stroke, from emergency to the long-term follow-up and giving some inputs on differential diagnosis, work-up, and treatment as linked to the symptoms and
findings which might alert the physician to it. For clarification, the reader is asked to consult the summaries of risk factors and investigations in the given tables. The information of this paper is based on published studies or consensus papers, but in case of missing information the current proceedings at the University Children’s Hospital in Bern including our own experience through the “Swiss Neuropaediatric Stroke Registry” (SNPSR) are described.

The Problem of Delayed Diagnosis

An important problem of childhood stroke is the delayed diagnosis.16–19 Missing awareness by parents and professionals of the possibility of a stroke already in children is a major concern. The second most important problem is the difficult differential diagnosis. Shellhaas et al (2006)20 could show that 21% of children presenting with suspicion of stroke had a different disease, in 60% of them a “nonbenign” etiology like seizures of different origin, posterior leukoencephalopathy, vascular anomalies, autoimmune inflammatory problems, infectious disease like abscess or encephalitis, brain tumor, drug toxicity or idiopathic intracranial hypertension. In contrary, Braun et al (2006)21 could show that in 19/45 of the children presenting with ischemic stroke primary suspicion was a nonstroke etiology and that in 5/45 etiology of stroke had to be revised after diagnostic work-up. The mean interval from initial to final correct diagnosis was 7 days (3 hours to 7 years), the change of diagnosis led to therapeutic changes in 17 patients. Thus, any child presenting with history and/or symptoms which might be due to an arterial ischemic stroke, should get an immediate work-up, to prove or rule out this diagnosis.

Signs and Symptoms at Manifestation

One of the reasons for the difficult primary diagnosis of stroke is certainly the variable symptoms and signs at manifestation (Fig. 1, SNPSR), which might occur at any age (Fig. 2, SNPSR). Thus, in the following section presenting symptoms of stroke, their differential, and their possible link to risk factors of stroke are going to be discussed. This might help a physician in emergency to realize the possibility of stroke and to initiate fast the most important steps of investigations.

A total of 70 to 80% of the children present with hemiparesis, with or without facial palsy, or dysphasia. Dysphasia in childhood is not limited to stroke of the dominant side, most likely due to the immature lateralization of language.22 Focal signs and symptoms are usually related to the localization of the ischemic lesion, however one has to be aware that also children with isolated thalamic stroke might present with hemiplegia and/or dysphasia. In contrast, ataxia is a typical symptom of an infratentorial stroke, but not limited to cerebellar lesions. Some children show nonfocal symptoms as headache, vomiting, or change of level of consciousness.2,5 Headaches are present in 30% of children, before, with or shortly after the onset of symptoms.5,23 Most important differential diagnosis are certainly hemiplegic migraine or dissection of carotid or vertebral artery. For the diagnosis of hemiplegic migraine, family or personal history and careful evaluation of presenting symptoms are most helpful. Hemiplegic migraine typically presents with a Jacksonian march of symptoms, which is different to the sudden onset of symptoms due to ischaemia.24 In our experience: children with hemiplegic migraine are frightened by their neurological loss of functions, but stroke patients show an astonishing neglect to their severe symptoms. Occipital headaches in children might be the first symptom of a cerebellar stroke and/or extracranial dissection. In the presence of an extracranial dissection the children might complain about ipsilateral pain of neck or face, in the presence of intracranial dissection about half-sided headache. The pain related to dissections is usually violent, nonpulsating, and lasting for hours or days. The focal neurological symptoms encountered are typically supratentorial in cases of carotid dissection and infratentorial (like cranial nerve dysfunction, Horner syndrome, diplopia, swallowing problems) in cases of vertebral dissections,25,26 although Horner and cranial nerve palsy can also be present in case of a carotid dissection.27 The dissection and therefore the pain might precede the acute ischemia by days, transient ischemic symptoms as warning signs are frequent. Mild to moderate changes of level of consciousness are present in one-third of children with ischemic stroke. They differ from hemorrhagic stroke, where loss of consciousness and coma are much more frequent.21 Total 20% of children with stroke present seizures during the first hours or days after stroke.28,29 It is our experience that seizures more frequently
occur during the first hours or days after the stroke, than actually at manifestation of the stroke, which is also supported by the paper of York-Corrales et al.\textsuperscript{30} \textit{Age at time of stroke} has an influence on possible symptoms: children <1 year are more likely to present with seizures and altered mental stage and children > 1 year with focal neurological signs.\textsuperscript{31}

**Neuroimaging**

The multifarious symptoms and the difficulties in diagnosis point to the importance of neuroimaging in a child with suspicion of childhood stroke, not only for diagnostic purposes, but also for evaluation of etiology and outcome.\textsuperscript{32,33} Computed tomography has the advantage of being readily available in emergency, but the disadvantage of missing out on early, small, or infratentorial ischemia. The golden standard is certainly magnetic resonance imaging with diffusion weighted images, revealing the ischemia within minutes and giving early on an accurate measure of the extension of ischemic area (\textsuperscript{Fig. 3}). T1, T2, and gradient echo sequences supplement the initial investigation.\textsuperscript{34} Early MRI with its diffusion and perfusion-weighted sequences is not only useful to detect ischaemia, but also for the differential diagnosis of many mimics of childhood stroke as acute demyelinating encephalopathy and hemiplegic migraine. Although CT is the emergency image of choice to search for a hemorrhage, acute hemorrhage can also be detected by MRI. Early MR also gives the opportunity to detect vasculopathies by a MR angiography (\textsuperscript{Fig. 4}). This is important in view of recent data showing that 53% of children with arterial ischemic stroke show arteriopathies.\textsuperscript{12} Inclusion of the neck vessels for imaging is
Figure 5. A 15-year-old boy presenting with acute right-sided hemiplegia. MR angio reveals severe stenosis of left sided medial cerebral artery (A) with significant recanalization 6 months later (B).

requested, as 25% of the children show lesions of cervical vessels.\textsuperscript{34} Best sequences for detection of dissections are a combination of (contrast-enhanced) MRA and nonfat and fat suppressed T1 weighted images of cervicocranial vessels.\textsuperscript{35} In view of the frequency of arteriopathy CT angiography might be equal to MR angiography, but both are known to miss the information from fat suppressed images.\textsuperscript{8,36} Vascular ultrasound is missing ~20% of dissections,\textsuperscript{37} but is an easy method for following up on vasculopathies. More accurate information for follow-up is available by MR angiography (\textsuperscript{\ding{51} Fig. 5}). Although conventional angiography is still the gold standard for detecting dissections and vasculitis, it is rarely performed in childhood stroke and has its indication for specific questions or in cases of endovascular treatments.

Risk factors

Published data over the last two decades have revealed that AIS has different etiological characteristics in children than in adults.\textsuperscript{1,3,5,10,12} Knowledge on childhood AIS risk factors has grown considerably in recent years and it has been shown that childhood stroke is a multiple risk factor problem.\textsuperscript{1,5,13} \textbf{Table 1} gives an overview on the many reported risk factors in childhood stroke, the leading symptoms, and primary investigations. However, knowledge of relationship between the various risk factors is still very limited, thus an evidence-based understanding of optimal treatment is still missing.\textsuperscript{10}

\textbf{Arteriopathies} can be detected in about half of the children after stroke.\textsuperscript{11,12,38–40} A total of 32% consist of the above discussed focal cerebral arterial arteriopathy (FCA) related to infection or postvaricella syndrome. A total of 22% are due to arterial dissection. Beside infection other triggers play a role in its occurrence: the most frequent is a (bagatelle-) trauma, but others such as cervical manipulation or skeletal abnormalities, homocysteinaemia and MTHRF mutations, connective tissue disease as Marfan syndrome, and migraine are also reported.\textsuperscript{25,41–43} Moyamoya (primary or secondary) is responsible for another 22% of arteriopathies and is the etiology of ~6% of childhood arterial ischemic stroke.\textsuperscript{38,44} It is characterized by progressive stenosis of the apices of intracranial internal carotid involving anterior and medial cerebral artery. Secondary Moyamoya can be seen in children with sickle cell disease, neurofibromatosis, and Down syndrome. The frequency of sickle cell disease in a childhood stroke population depends on the geographical area. In continental Europe sickle cell disease is rare. However, due to the possible prophylactic treatment it is important to detect early.\textsuperscript{23}

Primary arteritis of the central nervous system (PACNS) was thought to be rare, however recent work from Bensler et al\textsuperscript{45} suggests it to be underdiagnosed. Nonprogressive medium to large PCNS might be one of the etiologies for transient focal arteriopathies. Typically it shows by a stenosis of proximal medial cerebral artery with gadolinium enhancing wall thickening. CSF opening pressure is elevated, but cells and protein normal. Infectious etiology, especially varicella, has to be considered. Progressive medium to large vessel PACNS manifest by preceding symptoms as headache, cognitive dysfunction, and behavioral changes followed secondarily by a focal stroke. Imaging findings are similar to the none progressive medium to large vasculitis, but involve proximal and distal arteries and might include several vessel beds. Bilateral lesions are rare. Opening pressure of CSF is elevated, but in this form cells (lymphocytes) and protein are usually elevated. Small vessel CNS vasculitis is the classical form of PACNS with slowly progressive symptoms and the typical laboratory findings of vasculitis.

For children important risk factors are \textit{infectious and parainfectious etiologies}.\textsuperscript{5,46,47} Major infections such as sepsis and meningitis have long been recognized as risk factors for stroke. However, over the last two decades more and more reports on minor infections related to stroke have been published. Besides Varicella\textsuperscript{48} other pathogens as Borrelia, mycoplasma, enterovirus, and parvovirus\textsuperscript{1} are also thought to provoke cerebral ischemia. One of the important pathophysiology for infection triggered ischemia might be transient FCA. The current understanding is that a parainfectious reaction leads to a focal arteriopathy, as it is shown in a case of varicella zoster related focal arteritis.\textsuperscript{50} Recently, upper respiratory infections have been related to this transient arteriopathy, further supporting the parainfectious etiology.\textsuperscript{46} More and more information points to the idea, that an inflammatory reaction plays an important role in idiopathic childhood stroke.\textsuperscript{51,52} The most frequent etiology related to FCA is sickle cell disease, altered inflammation signaling plays an important role too.\textsuperscript{53} In addition, acute infection is shown to be a risk factor and potential trigger for spontaneous cervical artery dissection.\textsuperscript{42}

The second most important risk factor for childhood stroke are \textit{cardiac problems}.\textsuperscript{1,5} Peri-interventional insults remain frequently undetected, but catheter interventions have a significant risk of stroke.\textsuperscript{54} During heart operations, but especially during the days after the operation, children are at high risk for an embolic complication. Also for strokes related to cardiac problems co-risk factors as elevated lipoprotein a, MTHRF mutation, homocysteine, hereditary coagulopathies, or infections might be detected.

Rare, but important for a pediatric population are \textit{metabolic infarctions}.\textsuperscript{55,56} Energy depletion leads to ischemic lesions in mitochondrial problems. In urea cycle disorders (especially OTC), toxic deposits lead to destruction of cerebral tissue. For this reason, metabolic infarctions do not occur in a vascular territory, MELAS for example shows a predilection for occipital infarctions. Other metabolic problems such as Fabry disease lead to a focal arteriopathy, metabolic disorders...
### Table 1  Risk Factors and Investigations in Childhood Stroke (Second Variant)

<table>
<thead>
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<th>Summary of Risk Factors</th>
<th>Symptomatic Key</th>
<th>Diagnostic Investigations</th>
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<td><strong>Cardiac Problems</strong></td>
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<td>Cardiac Problems</td>
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<tr>
<td>Congenital malformations, cardiomyopathy</td>
<td>PH, clinical examination</td>
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<td>Endocarditis</td>
<td>General condition, fever, microemboli</td>
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<td><strong>Vasculopathy</strong></td>
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<td>Moyamoya</td>
<td>Recurrent episodes</td>
<td>MR-angiography, vascular sonography</td>
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<tr>
<td>Fibromuscular dysplasia</td>
<td>High blood pressure</td>
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</tr>
<tr>
<td>Arterial dissection</td>
<td>Minor trauma, infectionb</td>
<td>MR-angiography, fat suppressed MR-imaging, vascular sonography</td>
</tr>
<tr>
<td>Transient focal arteriopathy</td>
<td>Varicella, Borrelia, viral infection</td>
<td>MR-angiography, infection + vasculitis parameter, serologies</td>
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<tr>
<td><strong>Vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonprogressive medium to large vasculitis</td>
<td>Acute stroke</td>
<td>CSF opening pressure MR with focal enhancing vasculopathy</td>
</tr>
<tr>
<td>Progressive medium to large vasculitis</td>
<td>Progressive symptoms followed by acute stroke</td>
<td>CSF opening pressure, cells and protein MR with focal enhancing vasculopathy</td>
</tr>
<tr>
<td>Lupus, antiphospholipid-AB syndrome, systemic diseases, ZNS-vasculitis, others</td>
<td>Clinical symptoms</td>
<td>Elevated BSR, pathological coagulation (apPT), lupus AC, antcardiolipin AB, ANCA, other AB, MRI, MR-angio, SPECT</td>
</tr>
<tr>
<td><strong>Coagulopathies/Hematological Problems</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary coagulopathy</td>
<td>FH and PH, risk situation</td>
<td>Level 1 testing: factor V (Leiden), pro-thrombin, protein C, protein S, homo-cysteine, lipoprotein A, factor VIII level 2 testing: fibrinogen, factor IX + XI</td>
</tr>
<tr>
<td>Lupus-/antiphospholipid-AB-syndrome</td>
<td>Clinical findings</td>
<td>Anticardiolipin-AB, lupus anticoagulants</td>
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<tr>
<td>CDG-syndrome</td>
<td>Retinitis pigmentosa, dysmorphic features</td>
<td>Transferrin electrophoresis, MRI</td>
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<tr>
<td>Sickle cell anemia</td>
<td>Splenomegaly, anemia</td>
<td>Electrophoresis of hemoglobin, vascular ultrasound</td>
</tr>
<tr>
<td>Anemia, Iron deficiency</td>
<td>Paleness</td>
<td>Red blood count, ferritin</td>
</tr>
<tr>
<td><strong>Connective Tissue Diseases and Metabolic Problems</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danlos-syndrome</td>
<td>Hyperlaxity articulations and skin</td>
<td>DNA, skin biopsy</td>
</tr>
<tr>
<td>Marfan-syndrome</td>
<td>FH, marfanoid habitus</td>
<td>DNA, echocardiography</td>
</tr>
<tr>
<td>Mitochondrial problems (MELAS)</td>
<td>FH, failure to trith, multiorgan problem, occipital infarctions</td>
<td>Lactate (blood, CSF), mDNA, enzymes</td>
</tr>
<tr>
<td>Urea metabolic disorder</td>
<td>Acute/fluxuant neurological symptoms</td>
<td>AA, OA, ammonium</td>
</tr>
<tr>
<td>Molybdenum cofactor deficiency</td>
<td>seizures</td>
<td>Sulfite test in urine, AA in urine + serum, OA in urine</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Marfanoid habitus</td>
<td>AA in urine</td>
</tr>
<tr>
<td>Aminoacidemia</td>
<td>Acute or remittent neurological symptoms</td>
<td>AA (urine, serum, CSF)</td>
</tr>
<tr>
<td>CDG-syndrome</td>
<td>See above</td>
<td>Transferrin electrophoresis</td>
</tr>
<tr>
<td>Glutaric acidemia type I</td>
<td>Macrocephaly, hypoplasia temporal lobe</td>
<td>OA in urine, Tandem (carnitine profile) serum</td>
</tr>
</tbody>
</table>

(Continued)
might also lead to cardiomyopathy or rhythmic problem, which in turn might provoke an embolic ischemia.

The risk for stroke in children is increased by the presence of additional factors such as hereditary coagulopathy.\textsuperscript{57–60} The most relevant are antithrombin deficiency, protein C deficiency, elevated lipoprotein A, and antiphospholipid antibodies. Combination of the presence of hereditary coagulopathies doubles the risk of stroke.

In the last few years, more and more evidence has been detected that also iron deficiency or low ferritin might increase the risk of stroke.\textsuperscript{61} Preschool children are known to have an iron deficiency in 4 to 6%. Therefore, beside frequent infections, iron deficiency might be an explanation why preschool children have a high risk of arterial ischemic stroke.

**Investigations**

Although in the majority one or more risk factors for stroke in childhood can be detected,\textsuperscript{5} more exact pathophysiological knowledge, especially on interference of different risk factors is still not present. Thus, a thorough course of investigations in each child after AIS is suggested.

Neuroradiology is the first investigation. Special attention has to be drawn to perform all necessary sequences and to image not only head, but also neck (see above). Vascular ultrasound is an easy investigation to follow on known arteriopathies with stenosis, but has a limitation for detection especially for dissections.

A cardiac investigation with electrocardiogram to look for rhythmic abnormalities and an echocardiography to search for structural or functional abnormalities is mandatory. Whether children need beside a transthoracic echocardiography also a transesophageal echo is still a matter of discussion. A recent paper shows the limitation for transthoracic echocardiography including bubble echo’s to detect a foramen ovale with a sensitivity of 88%.\textsuperscript{62}

As pediatric stroke is a multiple risk problem, laboratory investigations should be performed on a broad basis, including always search for infections, vasculitis, thrombophilia, and metabolic problems. → Table 2 gives a suggestion on how to proceed with the necessary laboratory investigations.

**Controversies on Treatment**

Up to date, there are three guidelines on management of acute stroke in childhood.\textsuperscript{13–15} However, all three guidelines are not based on data from pediatric studies, but rather represent expert opinions or conclusions that have been drawn from adult studies. There is a broad agreement between professional about supportive treatment within the first few days: careful monitoring with body temperature $<36.5^\circ C$, blood pressure adjusted to cerebral needs, treatment of dyselectrolytemia, hypoglycemia, and seizures. Especially in children with large volume and/or infratentorial ischemia, there is a high risk of malignant swelling. Early decompressive surgery has to be evaluated in these children.\textsuperscript{63,64} Thus careful monitoring on an intensive care unit in those children is mandatory. Thrombolysis is shown to be feasible and successful in children.\textsuperscript{65,66} However, there is still missing evidence, that outcome of children can be influenced positively by this potentially also harmful treatment. There are few case reports, where children were successfully treated endovascularly by recanalization devices.\textsuperscript{67} The main discussion on acute treatment is heparinization versus aspirin. In the UK and American guidelines aspirin (3 to 5 mg/kg BW) is the treatment of choice, except for some special indications as cardiac embolism or extracranial dissection. In the chest guidelines heparinization during the acute phase till exclusion of cardiac problem or dissection is preferred over initial aspirin. In a study from Colorado and Germany, it was shown that anticoagulation during the first 4 weeks in children with arteriopathy (exclusion of Moyamoya) might be safe and worthwhile an evaluation.\textsuperscript{68} In an international

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**Table 1 (Continued)**

<table>
<thead>
<tr>
<th>Summary of Risk Factors</th>
<th>Symptomatic Key</th>
<th>Diagnostic Investigations</th>
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</thead>
<tbody>
<tr>
<td>Neurofibromatosis</td>
<td>Skin, typical signs</td>
<td>Clinical criteria for diagnosis, DNA</td>
</tr>
<tr>
<td>Sturge-Weber-syndrome</td>
<td>Skin</td>
<td>MRI</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Skin, typical symptoms</td>
<td>Alphagalactosidase activity, DNA</td>
</tr>
<tr>
<td>Homocystinuria, ischemia</td>
<td>See above</td>
<td>Homocysteine (urine, blood), DNA</td>
</tr>
<tr>
<td>Syndromes of progeria</td>
<td>Clinic</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Dyslipoproteinemia</td>
<td>Atheromas, arcus lipemic</td>
<td>Electrophoresis of lipids</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
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<tr>
<td>Heroin, cocaine,</td>
<td>History</td>
<td>Drug screening</td>
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<tr>
<td>sympathomimetic</td>
<td></td>
<td></td>
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<tr>
<td>Migraine</td>
<td>FH, PH</td>
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</table>

AA, amino acids; OA, organic acids; AB, antibodies; CDG, carbohydrate deficient glycoprotein-syndrome; FH, family history; PH, personal history.
observational study, the variety of practical approaches in treatment decisions all over the world have been illustrated. Aspirin in a dosage of 2 to 3 mg/kg BW for prophylactic treatment after the acute phase is accepted by most professionals.

### Outcome and Prognosis

For many decades, it was assumed that stroke in childhood is less devastating in children than in adults, concerning not only initial manifestation but also outcome. However, our recent study reveals that severity and outcome of arterial ischemic stroke in children and young adults (up to 40 years) are similar. Mortality in children is around 10 to 20%. In two-thirds of the children, lifelong handicap has to be expected. There are neurological residual symptoms in two-thirds of children. In the majority, these consist of hemiparesis with and without facial involvement and/or dysphasia; but ataxia, ophthalmological problems, seizures, and many more are also reported. However, most pronounced for these children and their families are lifelong neurocognitive and behavior problems. There is still only limited knowledge on prognostic factors for outcome. It has been shown that the long-standing belief that younger children have better prognosis has to be revised. Neuroimaging might play a major role for prognosis, but knowledge is still limited. The burden of possible recurrence of stroke should not be neglected. Risk of recurrence is between 10 and 20%.

In summary, there are many areas of limited knowledge and controversies in childhood arterial ischemic stroke. There is an urgent need of international and multicenter studies to gain knowledge, not only on treatment options, but also on natural course of the disease and prognostic factors.

### Acknowledgments

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### References

Arterial Ischemic Stroke in Childhood

Steinlin


