Cerebral Angiopathies as a Cause of Ischemic Stroke in Children

Differential Diagnosis and Treatment Options

by Hans-Jakob Steiger, Daniel Hänggi, Birgit Assmann, and Bernd Turowski

SUMMARY

Background: Ischemic stroke in children can present with an epileptic seizure or be initially asymptomatic. The median time to diagnosis is 24 hours.

Methods: This review is based on a selective literature search, with additional consideration of published guidelines and the authors’ personal experience.

Results: In Europe and the USA, the combined incidence of ischemic and hemorrhagic stroke in childhood is 2.5 to 10 per 100 000 children per year. 40% of ischemic strokes in childhood occur after an infectious illness or in association with a congenital heart defect, sickle-cell anemia, or a coagulopathy. Arterial dissection and chronic, progressive cerebral arteriopathies, particularly moyamoya disease, each account for up to 10% of childhood strokes. Magnetic resonance imaging can be used to demonstrate infarcts and to display the perfusion of ischemic areas and the surrounding brain tissue; arterial and venous occlusions can be defined more precisely. Children with arterial dissection, vasculitis, and para-infectious cerebral ischemia should be treated empirically, with medications and supportive care, according to the treatment plans developed for adults. For patients with moyamoya disease, surgical revascularization with extra-intracranial bypass techniques is recommended.

Discussion: The current data provide an inadequate evidence base for the treatment of stroke in children. Potential revascularization or thrombolysis must be discussed individually in each case. For the treatment of temporary, para-infectious cerebral ischemia, hemodynamic optimization is an available option. Better evidence is needed regarding the surgical treatment of moyamoya disease.

Cite this as


On average, an ischemic stroke in a child is not diagnosed until 24 hours after the event (1). Epileptic seizures are the most common clinical manifestation of cerebral ischemia in neonates and small children. For early intervention to be effective, referral to a specialized treatment center within a few hours of the event is essential (2). Current studies show that the incidence of stroke in children and adolescents in Western countries is as high as 10 per 100 000 persons per year (3, 4); 50% to 70% of these events are ischemic, and the remainder hemorrhagic (5). These current figures are more than twice as high as those from earlier decades. It must be assumed, however, that many cases never enter into the statistics, for a number of reasons: the manifestations of stroke in small children can be hard to detect, rich arterial collateralization can limit infarct size, and the high plasticity of the immature brain can enable functional compensation (6). Despite good collateralization and high plasticity, 90% of children who have sustained a stroke suffer from late sequelae including epileptic seizures and motor and cognitive impairment (7, 8). Many children who have sustained a stroke have a constellation of risk factors that can lead to recurrent infarcts if they are not detected in timely fashion and then definitively treated. In this article, we present the current concept of the evaluation and treatment of ischemic cerebral arteriopathies in children. This analysis is based on a PubMed search on the terms “pediatric” and “stroke,” with special consideration of the relevant guidelines of the American Heart Association (9).

The differential diagnosis of ischemic stroke in children

Cerebral ischemia in children is classified by etiology as cardioembolic, arterioembolic (due to diseases of the cervical arteries), or arteriopathic (due to diseases of the intracranial arteries) (8, 10–13) (Tables 1 and 2). Coagulopathies and heart disease are each present in 25% of children who sustain ischemic strokes (11, 14–16). Infection, the most frequent risk factor, is present in 40% of cases (14). The presumed mechanism is an infection-associated arteriopathy. No cause can be found in 10% to 20% of cases, and multiple risk factors are present in 20% to 30%, e.g., coagulopathy combined with infection.
Causes of ischemic stroke in children* (9)

<table>
<thead>
<tr>
<th>Entity</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Perinatal (embolism, infection, trauma)</td>
<td>25 per 100,000 live births (e29)</td>
</tr>
<tr>
<td>Arteriopathy due to infection</td>
<td>40% of ischemic strokes (11)</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>25% of ischemic strokes</td>
</tr>
<tr>
<td>Coagulopathies*</td>
<td>in 25% of ischemic strokes (e30, e31)</td>
</tr>
<tr>
<td>Trauma</td>
<td>10% of ischemic strokes (25)</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>6% of ischemic strokes (9)</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>30% of sickle-cell patients (in MRI) (e32, e33)</td>
</tr>
<tr>
<td>Chronic anemias*</td>
<td>often a cofactor accompanying other causes</td>
</tr>
</tbody>
</table>

*multiple possible causes in 20% to 30%, cause undetermined in 10% to 20%

Up to one-fourth of all children with heart disease will suffer an ischemic stroke (17). Children with complicated cyanotic congenital heart defects are particularly at risk (18), though stroke can occasionally occur as a consequence of acquired disease of the myocardium or the heart valves.

Perinatal ischemic stroke due to arterial hypoperfusion (occurring in the first week after birth) is usually due to infection and perinatal asphyxia; other causes include fertility treatments, chorioamnionitis, early rupture of the amniotic sac, and preeclampsia (5, 11, 19). In the neonatal period, both venous and arterial strokes are often characterized by focal epileptic seizures. Convulsions due to ischemia account for roughly 10% of epileptic seizures in infants born at full term.

The initial treatment and prognosis of ischemic stroke in children

When ischemic stroke is suspected, the diagnostic evaluation depends on the age of the patient, as well as on the available methods of examination. Cranial ultrasound is widely available but insufficiently sensitive to detect many cases of ischemia. Computerized tomography (CT) is a relatively quick and sensitive way to detect hemorrhage but can easily miss venous thrombosis and early arterial ischemia. Magnetic resonance imaging (MRI) can display zones of infarction, precisely define arterial and venous occlusions, and demonstrate the degree of reserve perfusion in the surrounding area. Catheter angiography is recommended in children only when there is a prospect of performing a therapeutic endovascular procedure (9).

It is recommended that all stroke patients be monitored and treated in an intensive care unit (9). In most cases, the treatment is conservative. Overall, children have a better prognosis after stroke than adults, and the risks of various therapeutic interventions in children, particularly thrombolysis, are insufficiently known. Treatment decisions are to be made on a case-by-case basis. 90% of the affected children suffer in the long term from cognitive impairment, spastic paresis, or epilepsy (8). Cognitive impairment without any other deficit is seen in up to 60% of patients. In children who have suffered a stroke because of arterial hypoperfusion, the average risk of recurrent stroke is roughly 15%; the risk of recurrent stroke in the individual case is largely a function of the constellation of causative factors that produced the initial stroke. In multiple large-scale studies, the risk of recurrent stroke was found to be highest in patients who carry a marker for a thrombotic tendency, e.g., a protein C deficit, in combination with a vascular disease, such as moyamoya (9, 16). Patients in whom a thrombotic tendency has been demonstrated should be treated, according to the current recommendations, with an inhibitor of platelet aggregation or with an anticoagulant drug (9, 20).

Secondary and transient cerebral arteriopathies

Infection is the most common risk factor for stroke in both neonates and older children (9) (Table 1). Pathophysiologically, stroke in such cases is usually due to involvement of the vasculature by local bacterial infection, e.g., meningitis or a local infection in the neck. Other infectious causes of stroke include septic embolization (e.g., in bacterial endocarditis), viral infection of an artery (e.g., with varicella-zoster virus [VZV]), and para-infectious vasculopathy (which may also be due to VZV). Vasculitis accompanies most types of intracranial infection; it is seen, for example, in tuberculous meningitis and in the aftermath of VZV infection. VZV can also cause necrotizing arterial infection: in such cases, transient intracranial vasculopathy may arise weeks or months after an uncomplicated episode of chickenpox. Transient vasospastic angiopathy has been described with increasing frequency in recent years (21) and can be caused by a variety of infections. VZV infection, in particular, seems to be a common trigger of transient, unilateral intracranial arteriopathy in childhood. As many as 30% of cases of purulent meningitis are complicated by ischemic stroke. Unilateral or bilateral occlusion of the internal carotid artery can be caused by necrotizing fasciitis in the parapharyngeal space. Fungal infection, which is more common in immunocompromised persons, can cause arteritis, aneurysms, thromboses, and cerebral infarction. Stroke has also been described as a consequence of various other infections of the central nervous system, including aspergillosis, Mycoplasma pneumoniae infection, Coxsackie 9 viral infection, California encephalitis, mumps, paramyxovirus infection, borreliosis, cat-scratch disease, brucellosis, and malaria (9). Transient angiopathy that has caused a stroke or transient ischemic attack (TIA) generally has a favorable prognosis for its further course, even without treatment. Anti-inflammatory medication is recommended in the acute phase (21). There is, however, a continuum of disease states ranging from transient angiopathy to necrotizing arteriopathy. Even non-necrotizing angiopathy, if hemodynamically significant, can cause progressive cerebral infarction. The advisability of therapeutic
anticoagulation or inhibition of platelet aggregation for four weeks is currently under discussion (7, 14, 20, 22).

**Autoimmune vasculitis in childhood**

Primary central nervous system (CNS) vasculitis is rarer in childhood than in adulthood. This entity is a granulomatous, necrotizing disease of blood vessels (23). It is difficult to diagnose because the systemic inflammatory and autoimmune parameters are often not very informative. Cerebrospinal fluid examination can reveal a high protein concentration (an inconstant finding) and lymphocytic pleocytosis. The MRI findings are abnormal in more than 90% of cases, yet they are often nonspecific and thus diagnostically unhelpful. Meningeal biopsy can be considered when the diagnosis remains in doubt. Primary CNS vasculitis takes a variable clinical course: some children reach a stable condition without any specific treatment, while others have progressive disease and must be treated with immune suppression (24).

Systemic diseases, such as lupus erythematosus, that more commonly affect adults are occasionally seen in children. Takayasu’s arteritis sometimes affects adolescent girls (9).

**Cervicocephalic arterial dissections in children and adolescents**

Acute cervicocephalic arterial dissection is an important cause of stroke in children and is probably underdiagnosed (25). It is estimated that up to 10% of ischemic strokes in childhood are due to dissection. Most dissections occur in the extracranial portion of the internal carotid artery, often as the result of blunt trauma (Figure 1). Intracranial dissection is rarer and usually spontaneous; its causes include fibromuscular dysplasia (FMD), Ehlers-Danlos syndrome, Marfan syndrome, aortic isthmus stenosis, polycystic kidney disease (e.g., MIM 173910, 173900), osteogenesis imperfecta, atherosclerosis, and moyamoya. Intracranial dissection manifests itself clinically either by ischemia or by subarachnoid hemorrhage. The angiographic criteria for dissection include the so-called pearl and string sign (a dilated vessel segment adjacent to a stenosis), a double lumen, and vascular occlusion with a pointed contour. High-resolution MRI can also reveal dissections; their detection by duplex ultrasonography is problematic, although this technique is often useful for follow-up of the lesion after it has been diagnosed. The affected artery becomes recanalized in about 60% of children, while the probability of a recurrent stroke or TIA is about 10%. The main goal of treatment in cervicocephalic arterial dissection is to prevent further thromboembolic strokes until the vessel is healed. The treatment of children and adolescents is based on that of adults with this condition and consists of immediate anticoagulation with intravenous heparin or a low-molecular-weight heparinoid drug, followed by 3 to 6 months of oral anticoagulation with a target International Normalized Ratio (INR) of 2. Anticoagulation should be given to a patient with an intracranial dissection only after subarachnoid hemorrhage has been excluded (9).

**Moyamoya disease and moyamoya syndrome**

Moyamoya disease is characterized by chronic progressive stenosis of the distal intracranial portion of the internal carotid artery; less commonly, there is additional involvement of the proximal portion of the middle cerebral artery, the anterior cerebral artery, the basilar artery, or the peripheral arteries of the brain (9, e1). Moyamoya is a Japanese word meaning “cloudy, like a puff of smoke.” This is a description of the typically nebulous angiographic appearance of the collateral arterial network that develops as a secondary feature of the disease (Figure 2). Traditionally, the condition is called moyamoya syndrome when it appears in association with some other disease, e.g., sickle-cell anemia or Down syndrome, and moyamoya disease when it is unaccompanied by any known risk factor. Moyamoya is rare in Western countries, with an estimated incidence of 0.1 per 100 000 persons per year, but it is ten times more common in Japan. It is presumed that many cases do not enter into the epidemiological statistics, because progressive stenosis of the basal arteries of the brain can also be clinically silent (e2). The diagnosis is made on the basis of radiological criteria (1): most often, there is stenosis of the distal portion of the internal carotid arteries on both sides of the brain and possibly also of the proximal portions of the middle and/or anterior cerebral arteries (2), combined with extensive arterial collateralization around the base of the brain (3) and bilateral abnormalities (e3). If angiographic abnormalities are found only on one side, the diagnosis is considered probable. Moyamoya disease accounts for about 10% of all strokes in children in Western countries and seems to be caused largely by genetic factors (e4, e5). Marked familial clustering has been observed; the disease

<table>
<thead>
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<th>TABLE 2</th>
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<tbody>
<tr>
<td><strong>Common cerebrovascular diseases in childhood (9)</strong></td>
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<tr>
<td>Entity</td>
</tr>
<tr>
<td>Moyamoya</td>
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<tr>
<td>Cervicocephalic arterial dissection</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td>CNS vasculitis</td>
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<tr>
<td>Post-varicella angiopathy</td>
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<tr>
<td>Associated with meningitis</td>
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<tr>
<td>Ergotism</td>
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<tr>
<td>Post-traumatic (injury, vasospasm)</td>
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<tr>
<td>Compression by tumor</td>
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<tr>
<td>Radiation-induced angiopathy</td>
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<tr>
<td>Congenital aplasia, hypoplasia</td>
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MEDICINE

is associated with the HLA B40 haplotype in children under age 10 and with the HLA B52 haplotype in older children. Moyamoya has also been linked to the AW24, BW46, B51-DR4, and BW54 antigens.

A Korean research team estimates that 50% to 70% of children with moyamoya disease who are treated conservatively go on to develop progressive neurological impairment and a poor clinical outcome (e6), while the rate of stroke in surgically treated children is 2.6% per year, according to a recent meta-analysis that involved a total of 1156 patients (e7). The prognosis of patients with moyamoya is a function of the rapidity and extent of vascular narrowing, the extent of neurological deficits, the presence or absence of effective collateral circulation, age, and the size of the infarct as seen by MRI (e8). Some authors consider the long-term outcome to depend mainly on the patient’s neurological condition at the time of treatment, rather than on the patient’s age (e9).

Many patients with moyamoya are treated with surgical revascularization, particularly patients with cognitive impairment or recurrent or progressive clinical manifestations (e10, e11). Revascularization can involve either a direct anastomosis, usually of a superficial scalp artery to a cerebral artery (Figure 3), or an indirect technique such as encephalo-duro-arteriosynangiosis or encephalo-myo-arterio-synangiosis. Procedures of the latter type are often preferable in children because the donor arteries of the scalp are of small caliber (e7, e12). They involve laying the temporalis muscle or the dural vessels directly onto the surface of the brain, so that arteries can sprout from these tissues and supply the brain with blood.

A number of authors have addressed the question of postoperative improvement of the prognosis after direct and indirect revascularization (e13–e15). A recent meta-analysis of children with moyamoya revealed that most patients benefit from treatment in terms of their clinical manifestations (e7). The meta-analysis included data on a total of 1448 patients from 57 studies. 73% underwent indirect revascularization, and 23% underwent indirect revascularization combined with direct anastomosis. In the perioperative period, 4.4% of patients had a stroke and 6.1% had a TIA. 87% of these children had a complete, or at least partial, reduction in new ischemic events; no difference in effectiveness was seen in this respect between direct and indirect techniques. For adult patients, in contrast, direct techniques were found to be much more effective.

Interestingly, surgical revascularization is performed in moyamoya disease not only when the patients present with ischemic stroke, but also when they present with intracranial hemorrhage. Its purpose in such cases is to prevent the further development of fragile collateral arteries at the base of the brain (e14–e17). The effectiveness of such procedures in preventing hemorrhage is less well documented than their effectiveness in preventing ischemic stroke.

Only a few studies have compared medical and surgical treatments for moyamoya. One study revealed that, among 651 moyamoya patients who were initially not operated upon, 38.4% went on to be treated with platelet
aggregation inhibitors because of progressively severe clinical manifestations (e14). Anti-platelet preparations have been used mainly to treat patients whose ischemic manifestations are thought to be due, at least in part, to thromboembolism. Coumarin derivatives have been used only rarely in children, but low-dose heparinoids have been used along with calcium-channel blockers as an empirical treatment for recurrent TIAs.

**Other vascular diseases**

Fibromuscular dysplasia (FMD) is a non-arteriosclerotic, segmental, non-inflammatory disease of blood vessels that usually affects the renal arteries and the extracranial segment of the internal carotid artery (e18, e19). Most persons with FMD are adult women, but cases of FMD in children and adolescents have been reported (e18–e21). Some 20% to 30% of FMD patients have cerebrovascular involvement, which is usually asymptomatic. Ischemic stroke can arise through stenosis or dissection of an affected artery, or through embolism. Intracranial aneurysms are found in about 7% of patients, but only a few cases of aneurysms in children with FMD have been reported. Surgical revascularization is recommended for symptomatic stenosis of the arteries supplying the brain (e22).

**Migraine**

The precise significance of migraine for stroke in children remains unknown. Migraine with aura seems to increase the danger of ischemic stroke in adolescents, particularly in girls taking oral contraceptives (e23). Migraine alone hardly ever causes ischemic stroke, but there is greater cause for concern when migraine with aura is combined with other risk factors such as cigarette smoking, pregnancy, or oral contraception. It is recommended that patients with migraine who have a stroke should be investigated for the presence of other risk factors, e.g., dissection, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), moyamoya, and mitochondrial encephalopathy with lactic acidosis and episodic strokes (MELAS) (e24).

Isoforms of three genes have been identified that are associated with familial hemiplegic migraine, and one of these genes encodes an ion-channel subunit (e25). Some children with familial hemiplegic migraine develop permanent neurological deficits; thus, children with this type of migraine seem to be at greater risk than children with other types. In view of the additional risk conferred by oral contraceptives, women with migraine who have suffered a stroke are advised to use another method of birth control instead (9). It is unknown whether triptans increase the risk of stroke in children, yet it seems prudent to avoid using these drugs in children with hemiplegic migraine, basilar migraine, known vascular risk factors, or previous episodes of cerebral or cardiac ischemia (e26). Options for prophylactic treatment include amitriptyline, valproate, cypéroheptadine, verapamil and other calcium-channel blockers, and aspirin (e26–e28). There is as yet no specific treatment for patients with CADASIL; platelet inhibitors can be considered for this indication (9).

**Conclusion**

Ischemic stroke does occur in children, though less commonly than in adults. It is often diagnosed only after a delay, particularly in small children. Recent decades have seen a number of diagnostic and therapeutic advances in the area of acute stroke, but children have benefited from these advances to a lesser extent than adults, because the existing data do not permit the formulation of any definitive pediatric recommendations. For moyamoya disease, which causes chronic, progressive cerebral ischemia in childhood, surgical revascularization is now accepted as the treatment of choice, although better validation of this is needed.

**Conflict of interest statement**

The authors declare that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.


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**KEY MESSAGES**

- On average, ischemic stroke in childhood is diagnosed after a delay of 24 hours.
- In neonates and small children, cerebral ischemia usually becomes clinically manifest through epileptic seizures.
- 90% of children who have sustained an ischemic stroke have lifelong impairment.
- 40% of strokes in children are due, at least in part, to an infection leading to transient or permanent disease of blood vessels.
- Moyamoya, a chronic and progressive disease of the cerebral vasculature, accounts for up to 10% of stroke among children in Europe. It is usually treated with surgical revascularization.
- A period of anticoagulation or platelet inhibition is increasingly being recommended for the treatment of children with transient angiopathies.
REFERENCES


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**REVIEW ARTICLE**

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