Arterial Ischemic Stroke in Neonates, Infants, and Children: An Overview of Underlying Conditions, Imaging Methods, and Treatment Modalities

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ABSTRACT

Conditions associated with arterial ischemic stroke (AIS) in children include congenital heart malformations, sickle cell disease, and meningitis, although around half of all cases are cryptogenic. Up to 80% of children with ischemic stroke have cerebrovascular disease, and case control studies demonstrate an association of arterial ischemic stroke in children with hereditary prothrombotic risk factors and infections such as *Varicella*. Conventional risk factors, such as hypertension and dyslipidemia, may also play a role and most children have several potential triggers rather than a single cause. Treatment recommendations are based on small case series or have been adapted from adult stroke studies; there are no evidence-based data on efficacy in children. Low-dose aspirin appears to be relatively safe. Anticoagulation with heparins, for example, low-molecular-weight heparin or warfarin, may be indicated in children with cardioembolic stroke, arterial dissection, or persistent hypercoagulable states, and blood transfusion has a role in patients with sickle cell disease. Tissue plasminogen activator has been used in a few patients within 3 hours of the onset of symptoms. At present, the benefit of treatment has to be weighed against the risk for each patient, but randomized controlled trials for primary prevention, acute treatment, and secondary prevention of pediatric ischemic stroke are urgently needed.

KEYWORDS: Arterial ischemic stroke, children, etiology, magnetic resonance, prothrombotic risk factors, therapy

Objectives: Upon completion of this article the reader should be able to (1) identify risk factors leading to peri- and neonatal ischemic strokes and (2) state some management options for these patients.

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Table 1 Conditions Associated with Ischemic Stroke in Childhood

Cardiac disease
Congenital heart disease
Infectious endocarditis
Cardiomyopathy
Arrhythmia
Hematological disorders
Sickle-cell disease
Thalassemia
Iron deficiency anemia
Inherited prothrombotic risk factors
Lupus anticoagulant/antiphospholipid antibodies
Lymphoproliferative disorders (CNS leukemia, asparaginase therapy)
Arterial vasculopathy
Transient cerebral arteriopathy/postvaricella angiopathy
Moyamoya syndrome
Fibromuscular dysplasia
Vasculitis, e.g., 2^0 to systemic lupus erythematosus/rheumatic diseases
Isolated angiitis of the central nervous system
Trauma
Dissection
Perforator shearing
Metabolic diseases:
Disorders of the lipid metabolism
Homocystinuria/ hyperhomocysteinemia
Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
Carbohydrate-deficient glycoprotein syndrome
Fabry's disease
Drugs
Cocaine
Oral contraceptives
L-asparaginase and steroids
Surgical interventions
Cardiac surgery/catheterization
Cerebral angiography
Extracorporeal membrane oxygenation (ECMO)
Neurocutaneous diseases
Neurofibromatosis
Sturge-Weber
Migraine
Hypertension
Infection
Meningitis
Varicella
Hypoxia/Ischemia
Obstructive sleep apnea/chronic hypoxemia
Hypotension

CNS, central nervous system.

Stroke in childhood has been recognized for centuries.[1] Cerebrovascular disease is at least as common as brain tumor in childhood, but has traditionally been considered difficult or impossible to treat, and so has received comparatively little attention. The estimated incidence is between 25 per 100,000 in neonates and 1.29 to 13.0 per 100,000 per year in children aged 1 to 18 years, with half of the cases due to ischemia.[2] Predisposing conditions for ischemic cerebrovascular accidents in children include congenital heart malformations, sickle cell disease, infections, and collagen tissue abnormalities (Table 1),[3–23] but around half occur in children who were previously well (cryptogenic stroke).[11] Up to 80% of children with ischemic stroke have cerebrovascular disease.[18,19,21,22] In addition, hypercoagulable states associated with a variety of prothrombotic risk factors also appear to be important.[24–43] There are a number of other possible risk factors for primary and secondary stroke in childhood which require further investigation, and it is becoming increasingly evident that stroke in childhood is frequently provoked by multiple risk factors. In pediatric patients with ischemic stroke, appropriate patient management is seriously hampered by the lack of clinical trials.[9,10] This article focuses on clinical presentation, underlying diseases, diagnostic imaging, and laboratory tools, as a consensus is emerging in these areas, and this will be important as we move forward to the essential multicenter collaborative studies. Therapeutic approaches are briefly discussed as a basis for the development of randomized controlled trials in children with stroke.[7,9,10]

CLINICAL PRESENTATION OF ARTERIAL ISCHEMIC STROKE AT ONSET

Ischemic stroke is defined as a focal neurological deficit lasting more than 24 hours with no cause other than that of vascular origin, although transient ischemic attacks, that is, neurological deficits lasting less than 24 hours, are commonly associated with infarction in children and many series have included these patients.[20] Neonates with arterial ischemic stroke (AIS) may present with lethargy, apnea, and/or seizures, often without other focal neurological deficits[40]: neurological signs may appear during the first year of life as motor skills develop.[40,44,45] In addition, seizures and decreased levels of consciousness are common presentations of stroke in younger children, particularly those under 4 years of age, although in most cases careful initial neurological examination reveals focal neurological deficits. Stroke in later childhood may manifest as hemiplegia, aphasia, or altered level of consciousness,[46] or as other focal neurological disturbances, such as visual and sensory impairment, or as ataxia in posterior circulation stroke.[47] Transient ischemic attacks frequently precede AIS in children. Headache is commonly associated and there may also be a clear history of recent infection (in particular *Varicella* in the preceding 12 months) or trauma.[48,49] Past medical, birth, and family histories should be taken carefully as these may provide clues to etiology.

DIFFERENTIAL DIAGNOSIS

Hemorrhagic stroke, which may require urgent neurosurgical intervention, must be excluded by emergency computed tomography (CT) or magnetic resonance imaging (MRI).[50] If available, MRI is very useful in the acute situation, either in excluding alternative pathologies or in confirming arterial disease. Venous sinus thrombosis may be accompanied by hemorrhagic or bland infarction, typically involving the frontal, parietal, or occipital cortex; MR venography usually demonstrates the occluded sinus. Metabolic stroke, for example, secondary to mitochondrial encephalopathy with lactic acidosis and stroke-like episodes or ornithine transcarbamylase deficiency, is relatively rare. There are often clinical clues such as persistent vomiting, and on neuroimaging the infarcts are usually not in a typical vascular distribution. The electroencephalogram (EEG) in hemiplegic migraine usually shows unilateral slow background activity. Acute disseminated encephalomyelitis is usually obvious on MRI and epilepsy with postictal hemiparesis may be diagnosed on EEG. In addition, it is important that the vascular pathology in AIS be defined so that conditions requiring urgent management, such as arterial dissection, are not missed.

CLINICORADIOLOGICAL PATTERNS

In children with cerebral infarction, one of the main issues regarding stroke mechanism is the differentiation between primary arteriopathy, embolus from an extracerebral location or a structurally abnormal heart, and sinovenous thrombosis. The correct vascular diagnosis may influence treatment and prognosis. Abnormalities of the cerebral arteries occur in up to 80% of children with AIS,[18,19,21,22] most commonly stenosis or occlusion of the large intracranial arteries, usually demonstrated on magnetic resonance angiography (MRA).[51,52] Rarely, there may be small vessel vasculitis, which may be missed by MRA. The pathogenesis of the stenosing arteriopathies is poorly understood, but is almost certainly a combination of genetic predisposition[23] and environmental triggers such as *Varicella* infection.[53] Radiologically, patterns include stenosis, occlusion, dissection, fibromuscular dysplasia, and moyamoya syndrome,[20] but preliminary natural history studies suggest that these groups are not mutually exclusive; for example, patients with dissection or stenosis at presentation may develop moyamoya collaterals at a later stage. However, most idiopathic stenoses are transient.[18] A strategy for neuroimaging is shown in Table 2.[19,50–52,54] If arterial dissection is suspected, MRI of the neck with fat saturation or MRA of the cervical arteries is mandatory. Conventional angiography should be considered in situations where MR angiography and venography are normal, small vessel disease is suspected, or dissection has not been excluded, and in children with posterior circulation infarcts or in those with unexplained recurrence.[19,51,52]

CARDIAC DISEASE

Cardiac disease (congenital cyanotic complex heart malformations or acquired heart disease) is a common underlying condition in children with ischemic stroke, both arterial and venous. Most of these children develop stroke in association with additional triggering risk factors such as cardiac procedures (surgery, biopsy, intervention) or noncardiac events (immobilization, other underlying diseases). The relative importance of previously undiagnosed cardiac lesions is controversial but electrocardiography and precordial echocardiography are essential investigations in any child with stroke; bubble contrast may be used during precordial or transesophageal echocardiography to detect intracardiac shunts, although poor cardiac function appears to be more common in children.[20]

Table 2 Neuroimaging and Cardiac Investigations in Children with Ischemic Stroke

Neuroimaging	Cardiac Investigations
CT (Computed tomography): To exclude hemorrhage	
Magnetic resonance imaging (MRI: T2-weighted for initial diagnosis, T1-weighted spin echo of neck with fat saturation)[1]	
Diffusion-weighted[2]	
Perfusion-weighted[3]	
Transcranial Doppler ultrasound[4]	
Magnetic resonance angiography (MRA)	Electrocardiography
Magnetic resonance or CT venography[5]	Transesophageal echocardiography
Conventional cerebral angiography[6]	Precordial echocardiography: bubble contrast

[1]T1-weighted spin echo of the neck with fat saturation sequence to exclude dissection.
[2]Diffusion imaging demonstrating areas of acute cytotoxic edema.
[3]Perfusion imaging to demonstrate areas of abnormal cerebral blood flow, blood volume, and mean transit time.
[4]Screening for arteriopathy may be undertaken using transcranial Doppler sonography of the intracranial vessels and duplex ultrasound of the neck.
[5]Venography may be indicated to exclude sinovenous thrombosis, particularly if the infarct involves the parietal or occipital cortex or thalamus.
[6]Conventional angiography if MRI and MRA are normal and dissection or vasculitis are still considered to be possible diagnoses, and in patients with posterior circulation arterial ischemic stroke.

OTHER RISK FACTORS

There has been relatively little research into conventional risk factors for stroke in adults,[11] as it has been assumed that these would be of little relevance to children. Although diabetes is rarely associated with vascular disease in childhood, the possibility of a role for passive smoking cannot be discounted and there appears to be an association between hypertension and vasculopathy.[20] Chronic hypoxemia is a risk factor for central nervous system events in sickle cell disease[54,55] and may play a role in other conditions, such as cyanotic congenital heart disease.[11] Anemia is also common, often secondary to iron deficiency,[20] and some children have disorders of the lipid metabolism.[42] Careful clinical examination and inspection of routine investigations are therefore important.

In addition to the underlying triggering factors mentioned above, acquired or inherited risk factors for endothelial dysfunction and thrombosis may play a role in the pediatric population with AIS.[24–43] The distribution of risk factors may, however, vary in different countries with respect to the ethnic population background,[20,33,38,42] the underlying disease, and the number of patients/controls investigated.[24,26,38,56,57] Thus, to estimate the individual patient risk, it is recommended that symptomatic patient groups should be investigated in comparison with age- and gender-matched healthy controls.[42] Based on the data obtained from case-control studies, at least the symptomatic subject should be screened in a specialized coagulation unit 3 to 6 months after the acute stroke onset for the prothrombotic defects listed in Table 3; to date, only protein C deficiency has been linked with recurrence.[58] All symptomatic children with thromboembolic stroke should also be screened for antiphospholipid or anticardiolipin antibodies and the presence of lupus anticoagulants, but although abnormalities are found in around one third of children,[59] there is no evidence of a link with recurrence risk.[60]

Table 3 Screening in Symptomatic Pediatric Patients Suffering from Ischemic Stroke (May Be Modified with Respect to Different Ethnic Population Backgrounds)

Plasma/Protein-based*,**	DNA-based**
APC-R (APC resistance)	Factor V G1691A
Protein C activity/antigen	Prothrombin G20210A
Free and total protein S antigen	MTHFR C677T
Antithrombin activity/antigen	
Lipoprotein(a)	Further potential polymorphisms
Fasting homocysteine	
Lupus anticoagulant/ antiphospholipid antibodies	
Fibrinogen (Clauss)***	
Plasminogen***	

*3 to 6 months following the acute stroke onset.
**Possible causes of thrombophilia.
***Potentially inherited causes of thrombophilia.
APC, activated protein C.

OUTCOME, RECURRENCE, AND TREATMENT

The overall risk of recurrent AIS in children ranges from 6 to 30%,[58–65] depending on etiology and on whether the definition is clinical or radiological. Most cases occur within the first 6 months but recurrent stroke and transient ischemic attack have been reported several years after the primary event.[51]

In the acute phase, apart from preventing fever, as infarct volume and outcome may be related to body temperature, there is no neuroprotective strategy currently available which could be recommended for use in children. Seizures should be managed appropriately and surgical decompression and/or intracranial pressure monitoring should be considered in children presenting in coma who have large middle cerebral or cerebellar infarcts. In children with sickle cell disease, acute exchange transfusion is strongly recommended, although this must be conducted slowly, as neurological deterioration has been reported.[66–68]

In patients with moyamoya syndrome, revascularization may be helpful in reducing the frequency of transient ischemic attacks, but there has not yet been a randomized controlled trial. Treatment with antiplatelet agents should be considered, as prothrombotic disorders are commonly associated.[69]

ANTITHROMBOTIC DRUGS

Ischemic stroke is frequently the result of intracranial arterial occlusion. In the acute phase of stroke, antithrombotic agents may promote intracranial arterial anastomosis, limit the spread of the thrombus, help its dissolution, and finally reduce the size of the infarction. Antithrombotic drugs may also prevent deep venous thrombosis in immobilized stroke patients as well as the early recurrence of embolic events. The major risks, however, are systemic bleeding and hemorrhagic transformation.

Antithrombotic strategies in adult stroke patients are based on specific stroke classifications: atherosclerotic cerebrovascular diseases, cardiac embolism, cryptogenic stroke, and stroke of other unusual causes, that is, prothrombotic states, dissections, arteritis, vasospasm, or drug abuse (5%).[70] Based on this classification, recommendations for stroke prevention after a first stroke onset of atherothrombotic origin, published by the Fifth ACCP Antithrombotic Consensus Conference in 1998, include antiplatelet agents, that is, aspirin and clopidogrel, whereas long-term oral anticoagulation is recommended for patients with a first cardioembolic cerebral event.[70]

In contrast, stroke types in children differ essentially from those in adults.[15] Established extracranial ca-

rotid atheroma is relatively rare, and although vasculopathy is common, the intracranial vessels are more commonly affected. Coronary heart disease and atrial fibrillation, which are associated with embolic stroke in adults, are also rare, and there is a wide variety of stroke mechanisms in children with congenital heart disease.[20] The well-established risk factors for stroke in adults, for example, age, cigarette smoking, and diabetes, are rarely described in children.[20] Prothrombotic risk factors have little importance as risk factors for stroke in adults.[71–74] In contrast, the factor V G1691A mutation, the prothrombin G20210A genotype, protein C, protein S, or antithrombin deficiency, mainly known as risk factors in venous thrombosis, may play a more significant role as risk factors for AIS in children and young adults.[24–43]

ALTEPLASE

In adults, thrombolysis is associated with a 10% risk of hemorrhagic transformation, and the results of administering alteplase beyond a window of 3 hours have been disappointing with only about 5% of patients fulfilling the criteria for treatment. Children with stroke may present for medical attention within the 3-hour time window.[75–77] However, because of the rarity of the disease, the absence of childhood stroke units, the low sensitivity of computed axial tomography to acute infarction, and the wide differential diagnosis in this age group, the final diagnosis is rarely made with any degree of certainty at this stage. On the other hand, mortality in children with AIS is lower compared with adult patients and most children presenting with stroke can probably expect to lead independent lives as adults. Therefore it is difficult to see a major role for thrombolysis in children at the present time, although it may occasionally be justified in children known to be at risk (for example, because of congenital heart disease) or in children suffering a stroke in the hospital.[78–81]

ANTIPLATELET AGENTS

Several controlled trials in adults have shown that antiplatelet agents as primary or secondary therapeutic options reduce the first occurrence of ischemic strokes as well as stroke recurrence. In two large trials in adults with ischemic stroke, aspirin appeared to be associated with a modest improvement in outcome, probably because of a reduction in early recurrence and perhaps in addition to its antipyretic effect. Besides aspirin, the use of dipyridamole, clopidogrel, as well as the platelet glycoprotein IIb/IIIa receptor inhibitor abciximab has been reported.[82–87]

The most commonly administered antiplatelet agents for children are aspirin and dipyridamole.[88–90] Aspirin administered acutely in a daily dosage of 3 to 5 mg/kg/day in children with stroke might reduce early recurrence. For long-term prophylaxis, the dose of aspirin can be reduced to 1 to 3 mg/kg, as there is little evidence of benefit from a larger dose in adults. Experience at a number of centers suggests that this approach is probably safe, although recurrence occurs in approximately 10% of patients on aspirin.[89] Monitoring with the in vitro bleeding time (platelet function analyzer: PFA-100) is useful in identifying nonresponders.[91,92]

Dipyridamole at doses of 2 to 5 mg/kg/day is occasionally used in children, sometimes combined with aspirin in patients suffering from moyamoya syndrome. In patients treated with dipyridamole the adenosine diphosphate-induced platelet aggregation can be used for monitoring.

Very rarely, the new thienopyridine clopidogrel in a dosage of 1 mg/kg/day adjusted from the adult fixed dose of 75 mg has been administered to children with ischemic stroke, especially when transient ischemic attacks precede or follow a first stroke onset. Adenosine diphosphate-induced platelet aggregation is the method of choice for clopidogrel monitoring.

Significant bleeding related to the use of antiplatelet agents is rare in children. The relatively low to medium doses of aspirin rarely cause side effects. Up to now, Reye's syndrome has not been described in children to whom low-dose prophylaxis has been administered, although influenza and perhaps *Varicella* vaccination might reduce this risk still further.

STANDARD HEPARIN

In a meta-analysis, administration of unfractionated heparin (UFH) in controlled trials in adult patients with stroke, either in low-dose regimens or at full dosage, significantly reduced the incidence of deep venous thrombosis and pulmonary embolism in the stroke patients treated.[93] In contrast, that analysis did not show a reduction in death rates in heparin-treated subjects, nor could it rule out the possibility that heparin increased the risk of hemorrhagic transformation. The dosage of UFH in children is 20 U/kg/hour for children over 12 months of age (maintaining antithrombin activity greater than 80% of normal age-dependent values) and 28 U/kg/hour in neonates and infants (Table 4). In children with stroke a loading dose of UFH should be avoided to reduce the risk of hemorrhage.[94] The target increase in activated partial thromboplastin time (aPTT) is 1.5-fold compared with baseline values or 0.4 to 0.7 U/mL antifactor Xa assay. Unfractionated heparin may be used in children with sinovenous thrombosis, AIS of cardioembolic origin, arterial dissection, or any other condition with high risk of early recurrence. A CT scan prior to heparin treatment is mandatory to rule out pre-existing intracerebral hemorrhage. As in adults, heparin-induced thrombocytopenia type II has also been reported in children.[95] Thus, platelet count monitoring in addition to aPTT measurement is mandatory.[96]

Table 4 Antithrombotic Drugs Commonly Used in Pediatric Stroke

Drug	High Dosage	Low/Medium Dosage	Monitoring
Antiplatelet agents			
Aspirin		3–5 mg/kg/day acutely (1)-3 mg/kg/day medium/ long-term	Optional: PFA-100
Antiplatelet agents			
Dipyridamole	—	2–5 mg/kg/day	Optional:
Clopidogrel	—	1 mg/kg/day (adapted from 75 mg/day in adults!)	ADP-induced platelet aggregation
Heparins			
Unfractionated heparin	20 U/kg/hour (> 12 months) 28 U/kg/hour (< 12 months)	— —	aPTT; platelet count; antifactor Xa assay
Heparins			
Low-molecular-weight Heparin: enoxaparin	1.0 mg/kg/bid (> 12 months) 1.5 mg/kg/bid (< 12 months)	1.0 mg/kg/day (> 12 months) 1.5mg/kg/day (< 12 months)	antifactor Xa assay
Oral anticoagulants	Individual dosage adjusted:		
Warfarin	INR 2.0–3.0 INR 2.5–3.5 (cardioembolic stroke)	—	INR

ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

LOW-MOLECULAR-WEIGHT HEPARINS

Clinical studies in adults have demonstrated several benefits of low-molecular-weight heparins (LMWH) over standard heparin. LMWH are as least as effective as UFH, the frequency of bleeding complications and heparin-induced thrombocytopenia is significantly lower, and, since the pharmacokinetics of LMWH are more predictable than those of UFH, the frequency of monitoring via antifactor Xa assays is minimized.[97–100] In addition, the relatively long half-life of LMWH allows for once- or twice-daily subcutaneous application. In a randomized, double-blind, placebo-controlled trial comparing two doses of LMWH with placebo in the treatment of ischemic stroke started within 48 hours of stroke onset, it was demonstrated that adult patients receiving LMWH had a better 6-month outcome with respect to stroke survival.[98] In that study, administration of LMWH was found to be safe, with no difference observed in the rate of hemorrhagic infarct transformation in the patients treated. The results of that study were not widely accepted, however, and the role of LMWH in stroke remains highly controversial.[101]

In contrast to adult patients, data recently reported in children with stroke indicate that prothrombotic risk factors mainly known as risk factors for venous thrombosis also play a role as risk factors for pediatric AIS.[24–43] Thus, LMWH, an appropriate drug in venous thromboembolism, may also have its place in stroke treatment during childhood and adolescence. Hemorrhage as a potentially fatal side effect of LMWH was not observed in children[89,102]; this may be due to underlying diseases and arterial wall structures differing between pediatric AIS patients and the elderly, thereby raising the question of whether LMWH have a better risk:benefit ratio in childhood compared with adult AIS. In addition, recently published experimental data in rats give evidence that standard nonhemorrhagic doses of one of the LMWH, for example, enoxaparin, have neuroprotective properties and reduce ischemic damage in previously healthy arteries.[103]

Pharmacokinetic studies in children have indicated that LMWH (enoxaparin) can be administered subcutaneously in high doses of 1.5 mg/kg (neonates and infants) or 1 mg/kg (children older than 12 months of age) *twice daily* or as a so-called prophylactic regimen *once daily*, respectively.[104,105] Monitoring via antifactor Xa activity is recommended for twice-daily administration. In addition, platelet counts should be routinely performed in order not to overlook heparin-induced thrombocytopenia, which has also been described, albeit rarely, in patients with LMWH administration. In a recent prospective but nonrandomized study with a cohort of 135 consecutively recruited stroke children aged greater than or equal to 6 months to less than or equal to 18 years, no significant difference was found between the use of aspirin and low-dose LMWH administered after a first symptomatic AIS with respect to incidence of stroke recurrence or drug-related adverse effects.[89]

ORAL ANTICOAGULANTS

In adult stroke patients, long-term oral anticoagulants appear to be effective in reducing embolism from cardiac sources such as rheumatic valvular heart disease, mechan-

ical prosthetic heart valves, and atrial fibrillation. A double-blinded, randomized trial comparing medium-dose warfarin and medium-dose aspirin administered as secondary prevention in adult stroke patients with nonoperable atherosclerosis (that is, excluding cardioembolism) showed no difference in preventing a second stroke.[106] Experience in children with long-term oral anticoagulation aimed at preventing cerebral vascular accidents is limited.[107,108] However, warfarin has been recommended on a case-by-case basis in children with stroke due to congenital or acquired heart disease, arterial dissection, and hypercoagulable states. The international normalized ratio (INR) is used to monitor warfarin therapy. An INR of 2.0 to 3.0 is appropriate for most children on warfarin, but in pediatric patients with mechanical heart valves an INR of 2.5 to 3.5 is recommended, and INR home monitoring is available.[109]

STRATEGIES FOR FURTHER STROKE STUDIES IN CHILDREN

International collaboration will be essential in estimating the distribution and impact of AIS in children. Similar imaging methods, laboratory investigations, and treatment modalities must be used and objective study endpoints should be prospectively defined. In order to avoid classification errors which may lead to spurious conclusions, it is very important to compare children with AIS from different countries or ethnic backgrounds with respect to underlying diseases, for example, acquired or genetic.

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