Recent developments in childhood arterial ischaemic stroke

Catherine Amlie-Lefond, Guillaume Sébire, Heather J Fullerton

Stroke is increasingly recognised as a cause of childhood disability and lifelong morbidity: population-based estimates of the annual incidence of childhood stroke (ischaemic and haemorrhagic) range from 2.3 to 13.0 per 100 000 children, and incidence rates in neonates are closer to 1 per 5000 livebirths. Stroke in childhood can have many causes. Diagnosis is often delayed owing to low clinical suspicion and the need to exclude the frequent mimics of stroke in childhood. Outcomes are related to presentation, associated illnesses, the underlying cause, size, and location of the infarct, and stroke subtype, but more than a half of the children who have had a stroke will have long-term neurological sequelae. Furthermore, estimates of recurrence rates range from 6–19% in the first few years. Arteriopathy—including arterial dissection and other progressive and non-progressive arteriopathies—might account for up to 80% of childhood stroke in otherwise healthy children. Because children with cerebrovascular abnormalities are at the highest risk of recurrence (66% at 5 years), understanding of the nature and course of these arteriopathies is crucial to the development of secondary stroke prevention strategies.

Introduction

Stroke in childhood has long been thought of as a rare and benign occurrence. However, advances in non-invasive neuroimaging have led to increased recognition of this disorder in children who might otherwise have received a diagnosis of hemiplegic cerebral palsy. Furthermore, the idea that children recover well from stroke has been contradicted by the results of outcome studies that show a high rate of lifelong morbidity: 10% of children who have a stroke die; 20% have further stroke; and 70% have seizures or other neurological deficits.1–3 The median cost of medical care in the first year after childhood stroke is more than $43 000, and the attendant health-care needs of these children can last decades. This Review will look at advances in the diagnosis, management, and prediction of outcome of childhood stroke.

Definition

The broad definition of paediatric stroke includes ischaemic and haemorrhagic stroke. Ischaemic stroke can be further subdivided into arterial ischaemic stroke and sinovenous thrombosis, whereas haemorrhagic stroke includes intracerebral and subarachnoid haemorrhage. Paediatric stroke can also be subdivided into perinatal stroke (stroke that occurs between 1 month and 28 weeks after birth)1 and later childhood stroke. The terms “perinatal” stroke and “neonatal” stroke are often used interchangeably in published work, although the term neonatal, by definition, applies only to events that occur after birth (ie, exclusive of in-utero events). Because it is frequently difficult to establish the timing of stroke, the term “perinatal” stroke is favoured by many investigators.

The aetiology, management, and outcome of paediatric stroke vary dramatically by stroke subtype and the age of the patient; however, owing to space limitations, this Review will focus on only one stroke subtype: childhood arterial ischemic stroke (AIS), which is defined as a cerebrovascular event that occurs between 1 month and 18 years of age. AIS is characterised by an acute-onset neurological deficit due to an infarct in an arterial territory consistent with the clinical syndrome.

Incidence and demographics

Population-based estimates of the annual incidence of childhood stroke (ischaemic and haemorrhagic) range from 2.3 to 13.0 per 100 000 children;4 the incidence rate in neonates is closer to 1 per 5000 livebirths.1 About a half of incident childhood strokes are ischaemic, and the incidence is higher in boys than it is in girls.5,6 Compared with white children, black children have higher stroke incidence and mortality, even after the exclusion of children with sickle cell disease.7–11

Clinical presentation of AIS in childhood

Hemiparesis is the most common presentation of AIS in childhood, and the middle cerebral artery territory is the most common location of infarcts in children.12–16 Other common presenting features include altered mental status and focal neurological signs, such as aphasia and visual disturbance.17 Stroke in the posterior circulation can present as ataxia, vertigo, or vomiting and is often mistaken by families and physicians for a viral infection. Younger children are more likely to present with encephalopathy and a decreased level of consciousness; however, on detailed neurological examination, younger children will usually also have a focal neurological deficit. Motor deficit is usually greatest on presentation18 but can also be progressive over a matter of hours or can wax and wane.19 The progressive onset of stroke symptoms is predictive of an underlying arteriopathy.10

The differential diagnosis for acute hemiparesis in a child includes complicated migraine, focal encephalitis, and focal seizure (ie, a postictal Todds paresis).20 Because seizures and headache commonly accompany AIS (as well as cerebral sinovenous thrombosis) in children, and the initial CT is often negative for true stroke, head MRI with diffusion weighted imaging (DWI) is often needed to differentiate a childhood stroke from a stroke mimic. Large-sized and medium-sized vessel arteriopathy usually presents with acute neurological deficits in...
stereotyped syndromes that are consistent with the occlusion of specific arteries; for example, a middle cerebral artery occlusion would typically result in weakness and numbness of the contralateral face and arm, with lesser involvement of the leg. Small vessel disease, which occurs much less commonly in children, is more likely to present with a neurological deficit of gradual and variable onset. Vascular lesions can be segmental, multifocal, and discontinuous, with deficits associated with partial or multiple vascular territories, which further confuses the clinical picture.23–25

Diagnosis
The diagnosis of stroke in childhood is often delayed and is rarely made within 6 h of symptom onset;26 even when evaluated by a child neurologist, stroke is uncommonly considered or diagnosed at the first assessment.23 Probable reasons for this delay include lack of clinical suspicion of stroke in the young and the frequency of stroke mimics in children, including migraine, seizures, encephalitis, and tumours. Nonetheless, more than three-quarters of children who are referred with suspected stroke to a well-established stroke team are ultimately diagnosed with stroke.22

Neuroimaging
The neuroimaging of stroke in adults has been well studied, and guidelines for appropriate imaging studies have been established.27 MRI is more sensitive than CT for the detection of AIS, particularly acute ischaemia and posterior fossa lesions (table 1). DWI can also detect cerebral ischaemia within minutes of onset (figure 1)—cytotoxic oedema results in a decreased apparent diffusion coefficient, which will be hyperintense on DWI—whereas perfusion weighted imaging (PWI) will show areas of decreased cerebral perfusion. Areas with normal DWI but reduced PWI (the so-called diffusion-perfusion mismatch) might be at-risk tissue that has not yet infarcted.28 However, the clinical usefulness of PWI in the routine management of acute childhood AIS has yet to be established.

Owing to the frequency of stroke mimics in childhood, a diagnosis of AIS requires confirmation of an ischaemic lesion. CT scans can miss early or small lesions and lesions in the posterior fossa; therefore, head MRI is recommended, but this might require the sedation of young or uncooperative patients. Ideally, DWI should be used but this is not available at all centres.

Brain MRI and magnetic resonance angiography (MRA) of the cervical and intracranial arteries are sensitive and non-invasive imaging modalities that should be the first step when investigating a suspected stroke. Vascular imaging is important owing to the high incidence of underlying cerebral arteriopathy in patients with AIS and the value of such imaging to predict the risk of stroke recurrence. Comparison between MRA and

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<td>Transcranial carotid doppler</td>
<td>Monitoring cerebral vasospasm after subarachnoid haemorrhage</td>
<td>Can be done at bedside; easily repeated; used to detect arteriopathy in patients with sickle cell disease</td>
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<tr>
<td>CT</td>
<td>Identify infarct by imaging of oedema and blood</td>
<td>Rapid and no sedation needed</td>
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<td>MRI</td>
<td>DWI and PWI can detect ischaemia within minutes of onset; gradient-echo imaging to image blood</td>
<td>More sensitive than CT to detect early stroke, particularly in posterior circulation; no radiation</td>
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<td>Cervical and intracranial MRA</td>
<td>Assess cerebral arteries</td>
<td>Sensitive for large vessel arteriopathy</td>
</tr>
<tr>
<td>Helical CTA</td>
<td>Assess cerebral arteries</td>
<td>More sensitive than MRA to detect intracranial stenosis and occlusion</td>
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<td>Conventional angiogram</td>
<td>The gold standard for the diagnosis of cerebral arteriopathy</td>
<td>More sensitive and specific than MRA to image arteriopathies, low risk of missing dissection or vasculitis, the diagnoses of which can alter treatment</td>
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MRA=magnetic resonance angiography. CTA=computed tomography angiography.

Table 1: Radiological approaches to detect cerebral arteriopathies

Figure 1: Acute infarction in the left middle cerebral artery territory
Infarction in the territory of the left middle cerebral artery is associated with restricted water diffusion, which appears bright on diffusion-weighted MRI (A) and dark on the apparent diffusion coefficient (ADC) map (B). Restricted diffusion lasts for 10–14 days and is helpful to time an infarction.
conventional angiography shows that MRA is as sensitive as conventional angiography in many cases. MRA seems to be equivalent to conventional angiography for the detection of vasculopathy of the internal carotid artery and the middle cerebral artery, although it is less sensitive for the detection of disease in smaller vessels.\textsuperscript{24,25,29} MRA has the advantages of no exposure to radiation and no requirement for intravenous access. However, MRA can overestimate the severity and length of stenosis.\textsuperscript{24,29} In adults, helical CT angiography is more sensitive than MRA for imaging intracranial stenosis and occlusion. Helical CT angiography might have fewer false-positive findings for stenosis and occlusion in the posterior circulation when there is minimal flow;\textsuperscript{19} however, this needs to be studied in children. The disadvantages of helical CT angiography in children include exposure to radiation, the need for intravenous contrast, and the difficulty in timing the contrast bolus in small children. Conventional angiography might be better before starting potentially risky treatments, such as surgical revascularisation in moyamoya syndrome. Conventional angiography is the gold standard for the diagnosis of cerebral arteriopathy and has a complication rate of between 0–1\% in children.\textsuperscript{31,32}

**Stroke location**

AIS in children usually involves the middle cerebral artery territory, and subcortical infarction (thalamus or basal ganglia) is common.\textsuperscript{31,32} Stroke in the posterior circulation is less common in children than stroke in the anterior circulation. In one report,\textsuperscript{9} most of the patients with stroke in the posterior circulation were boys with vertebrobasilar abnormalities, including arterial dissection. Lacunar stroke is rare in children.\textsuperscript{34}

**Risk factors and aetiologies**

Although many disorders have been associated with childhood AIS (panel), our understanding of the pathogenesis of AIS is limited. Most of the published work consists of hospital series; hence, the prevalence of different aetiologies is probably dependent on referral patterns at different institutions. Most population-based studies have had too few incident cases to shed light on the aetiologies that underlie AIS. In addition, the extent of diagnostic evaluation that is done varies greatly between reports. In the largest population-based study (97 cases of childhood AIS in northern California), the most prevalent aetiologies included primary cerebral arteriopathy (24\%), infection ([meningitis or sepsis] 23\%), and cardiac disease (12\%).\textsuperscript{13} More than a quarter of children (27\%) had no identifiable stroke risk factor, and this finding is supported by many hospital series, although it is highly dependent on the extent of the assessment of the aetiology.

The true prevalence of cerebral arteriopathy among children with AIS was probably underestimated in the Californian study because almost half of the incident cases did not have vascular imaging. Other data suggest that almost 80\% of otherwise healthy children who presented with first-time AIS have cerebral arteriopathy,\textsuperscript{16} which is a major risk factor for recurrent stroke.\textsuperscript{15} Thrombophilias have received considerable attention in the published work on childhood stroke but they are weak risk factors; hence, the role of individual

**Panel: Conditions associated with childhood AIS**

- **Cardiac**
  - Congenital heart disease
  - Endocarditis
  - Valvular disease (congenital or acquired)
  - Cardiomyopathy
  - Cardiac arrhythmia

- **Haematological**
  - Sickle cell disease
  - Thrombophilias (hereditary or acquired)
  - Iron deficiency anaemia

- **Cerebral arteriopathy**
  - Moyamoya disease (primary)
  - Moyamoya syndrome (secondary)
  - Down’s syndrome
  - Sickle cell disease
  - Neurofibromatosis type 1
  - Tuberous sclerosis
  - Post-cranial irradiation
  - Transient cerebral arteriopathy
  - Dissection
  - Post-infectious vasculitis
  - Fibromuscular dysplasia

- **Infections**
  - Varicella zoster virus
  - Bacterial meningitis
  - Neuroborreliosis
  - Mycobacterium tuberculosis
  - Fungal

- **Genetic**
  - Neurofibromatosis type 1
  - Tuberous sclerosis
  - PHACE syndrome
  - Fabry’s disease
  - Homocysteinuria

- **Toxic**
  - L-Asparaginase
  - Cranial irradiation

- **Malignancy**
  - Lymphoma
  - Leukaemia
  - Brain tumours

*Many children have multiple risk factors at the time of stroke.*
thrombophilies in the pathophysiology of AIS is unclear. Sickle cell disease is strongly associated with childhood AIS and accounts for a large proportion of the cases in stroke series of older children. However, the frequency of strokes in sickle cell disease has decreased dramatically with the advent of an effective primary stroke prevention strategy in 1998. Only 3% of the cases in the Californian study were due to sickle cell disease.

Cardiac disease
Cardiac disease is the cause of about a third of cases of stroke in childhood in some hospital series. Most children with a cardiac aetiology have previously been diagnosed with congenital heart disease. Almost any heart lesion can predispose to stroke; however, complex structural anomalies seem to confer the highest risk. Stroke in heart disease can occur spontaneously or during surgery or cardiac catheterisation.

Children with cardiac disease and stroke are more likely than controls to have higher lipoprotein (a) concentrations, the factor V Leiden mutation, heterozygous protein C deficiency, and anticardiolipin antibodies. Moyamoya syndrome is associated with congenital heart disease, and should also be included in the differential diagnosis of stroke in patients with congenital heart disease in syndromic (eg, Down’s syndrome, Williams syndrome, or neurofibromatosis type 1) or non-syndromic contexts.

Sickle cell disease
Sickle cell disease is a major risk factor for overt and silent stroke in children, and 11% of patients with sickle cell disease have had a clinically overt stroke by the age of 20 years. In the settings of deoxygenation, acidosis, or infection, sickle cell haemoglobin becomes denser, which causes the red blood cell to sickle. The sickled cells have increased adhesion to endothelium, which results in the formation of a thrombus. Sickle cell disease is associated with a progressive occlusive arteriopathy (a secondary form of moyamoya syndrome) that involves the supraclinoidal internal carotid arteries and proximal middle cerebral arteries, with relative sparing of the posterior circulation. Moyamoya-associated change is a risk factor for subsequent strokes despite transfusion therapy.

In patients with sickle cell disease, the incidence of ischaemic stroke peaks between age 2 and 5 years and that of haemorrhagic stroke between 20 and 30 years, which might represent a variable ability to generate collateral blood vessels to supply areas of ischaemic brain. The collateral vessels, commonly referred to as moyamoya vessels, probably protect against ischaemic events but predispose the patient to haemorrhagic stroke because they tend to be fragile. Hence, children who do not generate robust collaterals will present with ischaemic strokes at a young age, whereas children who do generate collaterals might present later with haemorrhagic stroke.

Other risk factors for stroke in sickle cell disease that have been described include raised blood pressure, lower haemoglobin concentrations, high leukocyte count, previous transient ischaemic attacks, priapism, acute anaemia, recent acute chest syndrome, or transfusion within the past 2 weeks. The mechanism of increased stroke after transfusion is unknown, but transfusion might alter blood viscosity or cerebral autoregulation. The increased prevalence of stroke among siblings with sickle cell disease, and the association with patients with multiple genetic loci, suggests a familial and genetic predisposition to stroke; stroke pathogenesis probably involves a genetic mutation, minor modifier genes, and environmental factors. Coexistent α-thalassaemia seems to protect against the abnormalities of large vessel arteriopathy, which can be seen with transcranial doppler ultrasound, but not necessarily against stroke.

Although stroke risk in children with sickle cell disease is high, this is the only setting in paediatrics where there is a proven method for primary stroke prevention. In children who are at a particularly high risk of stroke, on the basis of abnormal results on transcranial doppler, chronic blood transfusion therapy results in a 90% reduction in relative risk of stroke. Although highly effective, this stroke prevention strategy is problematic owing to problems of availability of transcranial doppler imaging, operator technique, poor patient adherence, and the side-effects, costs, and complications of chronic transfusions.

Other arteriopathies
Arteriopathy is increasingly recognised as an important cause of childhood AIS. The authors of a population-based study from California reported that of 52 children who had vascular imaging after AIS, 42% had stenosis due to arterial lesions, which were identified by clinical radiologists. A large study in the UK, which included careful vascular imaging in a hospital series of 185 children with AIS, found vascular abnormalities in 147 (79%); the most common intracranial abnormalities were occlusion or narrowing of the proximal large arteries, which was seen in 95 patients (64%). Although other groups have reported a similarly high prevalence of arteriopathy, the authors of a German study described a vascular aetiology in only 18% of 325 children with AIS. The inconsistencies in the results are probably due to the heterogeneous diagnostic approaches used and their respective sensitivities for arteriopathy. Infectious agents or inflammatory reactions triggered by infections seem to have an important role in the pathophysiology of these arteriopathies.

The types of arteriopathies seen in children are variable and include progressive and non-progressive disorders. In addition, although this designation includes disorders that have been well described in the published work, such as arterial dissection, moyamoya disorder, and vasculitis, many children simply have a focal stenosis in a large cerebral artery, a condition that is not well understood. This focal stenosis is typically unilateral and located in either the distal internal carotid...
or proximal middle cerebral arteries; however, different investigators have applied various labels to the same angiographic appearance (figure 2). Probably the most widely accepted label is transient cerebral arteriopathy, although serial vascular imaging showed that non-progression after 6 months is required to make this diagnosis. In the original series of nine patients with transient cerebral arteriopathy, all had idiopathic or post-varicella focal stenosis of the arteries of the circle of Willis, most commonly the proximal middle cerebral and distal internal carotid arteries, and less commonly the proximal anterior and posterior cerebral arteries. The term transient was used because in all nine patients the underlying pathophysiological process was monophasic and did not progress or recur after the first 6 months. However, the stenotic lesions were rarely transient and were all dynamic on serial imaging. Five of the nine patients showed initial progression over 2 to 7 months; on final imaging, done at 5 months to 2 years after initial imaging, two patients had complete resolution, five patients showed improvement, and two patients stabilised after initial progression. A larger series of 35 children with this idiopathic focal cerebral arteriopathy had a similar vascular distribution (predominantly the M1 segment of the middle cerebral artery) and similar development over time (complete resolution of the stenotic lesion in one patient, improvement in 24 patients, and progression or stable stenosis in 11 patients). A proportion of these patients have what is now called post-varicella arteriopathy of childhood.

Transient cerebral arteriopathy is a provisional diagnosis that does not specify an underlying pathophysiology; the aetiology of transient cerebral arteriopathy of childhood is unknown beyond varicella zoster virus arteriopathy but anecdotal observations implicate other infectious disorders, such as borrelia or enteroviruses. The persistence of the stenotic lesion for months to years in most cases makes vasospasm unlikely. In addition, the occasionally beaded and irregular appearance of the stenosis on angiography has led several authors to suggest that it is a focal vasculitis. Intracranial dissection might also be the cause of some cases of transient cranial arteriopathy. One group of investigators (predominantly rheumatologists) applied the term primary central nervous system vasculitis in children (pPACNS) to this focal cerebral arteriopathy, although this label might be presumptive owing to the lack of pathological confirmation of inflammatory cell infiltration of the vessel walls. These investigators showed systemic inflammation (raised erythrocyte sedimentation rate and C-reactive protein concentrations) in most patients and CSF inflammation in about a third. However, these children were studied at the time of their acute strokes; therefore, the inflammation might have been the end result of the infarction, rather than a cause of arteriopathy.

Children can also have congenital arteriopathies that predispose them to arterial ischaemic stroke. Examples include the dysplastic cervical and cerebral arteries seen in children with PHACE (posterior fossa brain malformations, facial haemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities) syndrome (figure 3).

Stroke associated with varicella zoster virus infection
An association between varicella zoster virus and stroke in children has been suggested by the authors of several paediatric studies, including one case-control study that showed that children with stroke were 18 times more likely to have had chicken pox in the previous 9 months than healthy controls were. Secondary reactivation of varicella zoster virus is also associated with stroke, and

Figure 2: Focal right middle cerebral artery stenosis in a teenage boy who presented with paroxysms of left hemiparesis and headache
(A) The stenosis was first seen on MRA as a loss of flow-related signal in the left MCA. (B) The stenosis was confirmed with conventional angiogram. The lesion remained unchanged over 6 months.

Figure 3: A congenitally dysplastic left internal carotid artery seen on MRA in an infant with PHACE syndrome
stroke has been reported in two children after varicella vaccination.7 In a series of children with AIS, those with a history of varicella zoster virus infection were more likely to have basal ganglia infarcts, abnormal cerebrovascular imaging, and recurrent AIS or transient ischaemic attacks than those without.8

The probable mechanism of stroke in varicella zoster virus infection is arteriopathy as a result of invasion of the meninges by the viral pathogen, with secondary invasion of the virus and inflammatory cells into segments of the wall of the large cerebral arteries that are adjacent to the CSF. Active varicella zoster virus replication in the CNS has been confirmed by PCR or by antibodies in the CSF.72

**Moyamoya**

Moyamoya is a progressive bilateral stenosis of the arteries of the circle of Willis with development of collateral blood flow. Moyamoya can be either primary (idiopathic), in which case it is referred to as moyamoya disease, or secondary to underlying disorders, in which case it is referred to as moyamoya syndrome. The underlying disorders include sickle cell disease, Down’s syndrome, and neurofibromatosis type 1. Moyamoya usually presents with recurrent, clinically overt ischaemic events; however, seemingly asymptomatic moyamoya syndrome can cause silent cerebral infarctions as well.73

The primary form of moyamoya is most common in children of Japanese and Korean descent, although it has been seen in children of many ethnicities. The aetiology of moyamoya disease is unknown, but a predominance in women, an east Asian distribution, and familial cases of moyamoya disease imply the existence of genetic risk factors.74 The mode of inheritance of familial moyamoya disease appears to be autosomal dominant with incomplete penetrance; transmission is predominantly maternal, and affected mothers were more likely to have late-onset or asymptomatic female offspring, which suggests the possibility of genomic imprinting.75 Multiple loci have been implicated in familial moyamoya disease.76–78

**Arterial dissection**

Dissection of the cervical or intracerebral arteries is an important cause of AIS in children that is diagnosed in up to 20% of cases in hospital series.79 The cause is typically an embolism that results from the migration of a thrombus that is originally located at the site of the subintimal dissection. Intracranial dissections are uncommon in adults, but a systematic review of the published work found they account for 60% of paediatric anterior circulation dissections. Intracranial dissection, like extracranial dissection, can be associated with trauma (major or trivial); however, a child with severe trauma is more likely to have an extracranial rather than an intracranial dissection.80

Although cephalic and cervical pain are the most common presenting features of arterial dissection in adults, only half of paediatric patients report headache, and neck pain is rarely reported.79 Furthermore, although up to a half of arterial dissections in adults are diagnosed before an ischaemic event,9 all the children in the systematic review had had an ischaemic event (stroke or transient ischaemic attack) before the diagnosis of their dissection. The failure to detect dissections in children before an ischaemic event could be related to the low incidence of pain, which might lead to diagnostic assessment, or a low index of suspicion for dissection in children who do present with pain.

An indirect effect of infection on the blood vessels is suggested by the association between antecedent acute infection and spontaneous cervical artery dissection. The results of case-control studies in adults suggest that ischaemic stroke in the setting of a recent acute infection is associated with about three times the likelihood of an underlying cervical arterial dissection.81,82 This association was independent of coughing, sneezing, or vomiting, which suggests an indirect effect of recent infection on blood vessels that is not fully explained by mechanical stress.82

**Thrombophilias**

The incidence of thrombophilia is increased in children with stroke; however, the importance of thrombophilia in stroke pathogenesis in children is still undefined. Thrombophilias that are associated with childhood stroke include increased lipoprotein (a) concentration, protein C deficiency, prothrombin 20210G→A rearrangement, methylenetetrahydrofolate reductase TT677 mutation, factor V 1691G→A mutation, and the presence of anticardiolipin antibodies.10,41,84–86 However, individually, these conditions are mild risk factors for childhood stroke, with odds ratios that typically range from 4 to 10, and results vary from study to study. Even if a thrombophilia was associated with an odds ratio of 10 or 20, because childhood stroke is so rare at baseline, the risk of stroke would still be extremely low. A single thrombophilia does not fully explain a stroke in a child, but multiple thrombophilias40,82 and thrombophilia in patients with cerebral arteriopathy76 or congenital heart disease confers a higher risk of stroke.4

**Acute management**

There are no data with regard to the acute management of childhood stroke; hence, management strategies are extrapolated from those developed for adults. Current recommendations include aggressive management of fever and maintenance of normoglycaemia and normovolaemia. Management of hypertension is controversial owing to concerns about the lowering of perfusion pressure; however, extreme hypertension is typically treated because of concerns for haemorrhagic transformation of the infarction. Seizures and infection should be aggressively treated and, in some cases,
treatment of the cerebral oedema and the increased intracranial pressure might be needed.96

Immediate treatment with antithrombotic drugs is commonly used to prevent recurrent ischaemic events in the acute setting. Aspirin is often the default antithrombotic, whereas anticoagulation with heparin or warfarin is reserved for emboli of cardiac origin or for arterial dissections. However, because of the lack of evidence there is considerable variability in practice.

Although hyperacute stroke therapies, such as intravenous alteplase, are being used for childhood stroke,88 their use is unstudied and controversial in children. In the original NINDS study, intravenous alteplase given to selected adult patients within 3 h of stroke onset improved neurological outcome despite ten times the risk of symptomatic intracerebral haemorrhage.89 Although there are several reports of intravenous alteplase being used in children as young as 2 years,81 the safety and efficacy of alteplase for acute stroke in children have not been established. Children probably have better spontaneous stroke recovery than adults; therefore, we cannot assume that the benefits of alteplase in children will outweigh the risks. Furthermore, because of developmental differences in the coagulation system of children, we cannot extrapolate from the dose used in adults. Studies in children to establish the safety and efficacy of intravenous alteplase are needed.

Stroke in children with sickle cell disease is treated with intravenous hydration and supplementary oxygen. Simple transfusion is recommended if the haemoglobin concentration is less than 10 g/dL, and this should be followed by erythrocytapheresis or exchange transfusion to reduce the percentage of sickled haemoglobin to below 30%.90

Recurrence

The authors of only three studies have done survival analyses to determine the rates and predictors of recurrent AIS in children: the 5-year cumulative recurrence rate was 5% (no CI reported) in a German study compared with 19% (95% CI 12–30%) in a Californian study and 18% (11–25%) in a UK study.11,13,91 Other studies have also reported a high proportion of children with recurrent AIS, although the length of follow-up was variable and was not included in the reported rates (22% in Chabrier and co-workers;99 19% in Lanthier and co-workers;80 23–8% in Barreirinho and co-workers;99 23% in Delsing and co-workers;99 14% in Ganesan and co-workers80). These recurrence rates do not show the true natural history but rather the rates despite current medical practice because most children in these studies were treated with antithrombotic therapy (aspirin or anticoagulation). Abnormal vascular imaging (ie, an arteriopathy) is a strong predictor of recurrence: in the Californian study, the 5-year cumulative recurrence rate was 66% in children who had a stenotic vascular abnormality compared with none of the children who had normal vascular imaging; and in the German study vascular aetiology and multiple stroke risk factors predicted recurrence.99 Children with sickle cell disease also have a high risk of recurrence; despite transfusions, about 20% will have a second stroke.96

Long-term management

The primary goal of long-term management is to prevent recurrent stroke (table 2), although there have been no trials of secondary stroke prevention in children who have had a stroke. Because of the high rates of recurrence, antithrombotic drugs are often used in children. The recurrence rate in untreated children can be as high as 50%;99 however, there are no data or consensus to guide the specific choice of therapy. The only published guidelines were created by the ACCP (American College of Chest Physicians) within a larger document on indications for the general use of antithrombotics in children.96 In addition, the UK Royal College of Physicians has published an online set of guidelines for childhood stroke. Both sets of guidelines refer to the low quality of available evidence but recommend anticoagulation for arterial dissection and cardioembolic stroke and aspirin for all other causes.

Aspirin at doses of 1–5 mg/kg/day has been used for secondary stroke prevention in childhood AIS, but there have been no controlled trials in children. Aspirin inhibits the enzyme cyclooxygenase and prevents the production of thromboxane A2, which is a platelet agonist; however, there is increasing evidence that aspirin might have additional antithrombotic effects that are independent of cyclooxygenase. Aspirin resistance (recurrent thrombosis despite the use of aspirin) is not uncommon but it is not clear how measurements of ex-vivo platelet function and the biochemical effects of aspirin can predict recurrent thrombus.87

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<tr>
<td>Moyamoya</td>
<td>Indirect vascular bypass: encephaloduroarteriosynangiosis (EDAM)</td>
<td>or encephaloduroarteriosynangiosis</td>
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<tr>
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<td>Chronic blood transfusions in children who have blood velocities of &gt;200 cm/sec on transcranial Doppler*</td>
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<td></td>
<td>Warfarin</td>
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*Class A evidence; no other stroke prevention strategies in childhood have been studied in a systematic manner. ** Currently being studied in a randomised, case-control study.

Table 2: Treatment options used for the prevention of stroke or stroke recurrence in children
Clopidogrel inhibits platelet aggregation and was well tolerated in a small case series of 17 children at doses of 1 mg/kg, to a maximum of 75 mg/day. Two of the nine children who received aspirin and clopidogrel developed subdural hematomas; both children, however, had cerebral atrophy, which probably predisposed them to the formation of subdural hematomas.

Sträter and colleagues reported on a series of children who received aspirin versus low-dose, low-molecular-weight heparin to prevent stroke recurrence. Although the observational study design precludes any conclusions about efficacy, the authors showed the relative safety of both treatment options.

Chronic blood transfusion to maintain sickled haemoglobin at less than 30% reduces the risk of secondary stroke to about 20% in patients with sickle cell disease. Despite the beneficial effects of transfusion, it is expensive and is associated with potential complications, including alloimmunisation and autoantibody formation, recurrent stroke while on transfusion, and iron overload, which can be treated by chelation with desferoxamine. Poor patient adherence is also a problem: the therapy is time-consuming for patients and their families. Stopping the transfusion in patients whose doppler readings have normalised results in a high rate of reversion to abnormal blood flow velocities and stroke.

Hydroxyurea reduces the sickled cell fraction and improves erythrocyte survival by inducing production of fetal haemoglobin. Children with sickle cell disease and stroke might be able to discontinue chronic transfusions and use hydroxyurea therapy to prevent stroke recurrence. Successful bone marrow transplantation, particularly from an HLA-matched sibling, can stabilise or improve cerebral arteriopathy and decrease stroke recurrence.

Encephaloduroarteriomyosynangiosis, with or without superficial temporal artery to middle cerebral artery anastomosis, might be more effective than encephaloduo-arteriosynangiosis for moyamoya vasculopathy.

Outcome

More than a half of children with AIS will have neurological sequelae. Infarcts in both hemispheres have been associated with poor outcome, but haemorrhagic infarction, the number of infarcts, and the size of the artery involved were not predictive factors. Seizure at stroke onset has been suggested as a negative prognostic factor but a larger study did not support this. Children with altered mental status on presentation and with complete middle cerebral artery cortical strokes have a less favourable prognosis.

Mortality from childhood stroke in the USA has decreased during the past 20 years. Black children have a higher risk of death from stroke of all types (ischaemic and haemorrhagic) than do white children, and boys are more likely than girls to die of haemorrhagic stroke.

A study of the long-term outcome of 20 children who survived stroke showed that 11 had a good outcome and a normal quality of life, whereas nine had a poor overall outcome with considerable neurological deficits; furthermore, younger age at the time of stroke was a risk factor for poor outcome. In a series of 44 children with AIS, 18 had residual dystonia and dyskinesia. The laterality of stroke does not influence neuropsychological outcome, and there is no clear relation between the location of stroke and cognitive outcome. Intellectual impairment is common in children with stroke that is associated with sickle cell disease.

Left-sided subcortical infarcts that affect the lenticular and thalamic nuclei or the internal capsule are associated with aphasia that persists. Attention is impaired after childhood stroke, and poorer performance is associated with an earlier age of stroke. Children who survive AIS will probably be at increased risk of cognitive and neurological sequelae as they get older, owing to decreased biological reserves in the brain.

Conclusion

Childhood arterial ischaemic stroke is an important cause of childhood morbidity. The prompt recognition of stroke and thorough investigation for potential risk factors are crucial. Vascular imaging is of particular importance for identifying those children at high risk of recurrent stroke. Advances in our understanding of the pathophysiology of childhood stroke will optimise the primary prevention of stroke in high-risk children and prevent stroke recurrence.

Search strategy and selection criteria

The information for this review was identified by searches of PubMed for publications between 1966 and October, 2007, with the terms “stroke and child”, “stroke and childhood”, “cerebral infarction and child”, “stroke and imaging”, “child and neuroimaging”, “stroke and sickle cell”, “sickle cell and treatment”, “stroke and treatment”, “stroke and thrombophilia”, “stroke and vasculopathy”, “brain and vasculopathy”, “stroke and varicella zoster virus”, and “vasculopathy and varicella zoster virus”. The searches were updated in December, 2007. Additional references were obtained from the bibliographies of manuscripts identified through our searches. Only publications in English were reviewed.

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Contributors

All authors contributed equally to the preparation of this manuscript.

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Conflict of interest

We have no conflicts of interest.


