CURRENT TOPIC

Stroke in childhood

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Presentation with stroke is rare in children, with an incidence of 2.6 and 3.1/100 0000 white and black children, respectively.[1] Half are haemorrhagic, requiring immediate transfer to a neurosurgical unit in case decompression is required. Traditionally, ischaemic strokes have been considered to be idiopathic and to have a good prognosis, with a low recurrence risk and good recovery of motor function and school performance. They have not been investigated extensively, on the basis that management would not alter. However, there is a significant mortality,[1] as well as considerable morbidity and a risk of recurrence, none of which has been adequately defined epidemiologically. In addition, there is now evidence that the neurological outcome could be improved, at least in some subgroups, by appropriate emergency management and, particularly, that recurrence might be preventable. This article proposes essential investigations and management for "good practice" in the current state of knowledge, although further research is clearly required before evidence based guidelines can be produced.

Definitions

A focal neurological deficit lasting more than 24 hours is defined as a stroke if it has a vascular basis, while a similar episode lasting for a shorter period of time is considered to be a transient ischaemic attack. The term "reversible ischaemic neurological deficit" has been coined to cover those episodes where deficit lasts more than 24 hours but the patient eventually recovers fully. This is an important concept in the context of treatment trials, but is difficult to predict when the patient first presents. The differential diagnosis in a child presenting with an acute hemiparesis includes tumour, traumatic extradural or subdural haematoma, central nervous system infection (focal encephalitis, abscess), and demyelinating conditions such as acute disseminated encephalomyelitis, as well as Todd's paresis and migraine. The concept of a "stroke-like episode", a focal neurological deficit lasting more than 24 hours without an obvious vascular abnormality, is a useful one in paediatrics because, even with full investigation, 10–20% of children with an apparent focal ischaemic event will not have evidence for vascular disease. In some of these, a tentative diagnosis may be made (for example, hemiplegic migraine, hypertensive encephalopathy, or "metabolic stroke"), but in others, the cause remains obscure. The term Todd's paresis is usually best avoided if the neurological deficit persists for more than one hour because important pathology might be missed. In children, it is always tempting to assume that the deficit will recover fully, although the evidence suggests that if the diagnosis is ischaemic stroke, this is rarely the case. Modern imaging techniques are challenging the traditional clinical concepts. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for the diagnosis of infarction within 24 hours, and is comparable for the diagnosis of haemorrhage.[2] It is now clear that, although most patients with prolonged clinical deficits eventually have infarction on neuroimaging, similar but clinically and radiologically reversible syndromes may occur—for example, in severe hemiplegic migraine; contralateral electroencephalogram (EEG) slowing and a scan showing oedema without infarction are clues to the diagnosis.[3] On the other hand, patients with short lasting neurological syndromes or even with no clinical symptoms at all may have suffered infarction, sometimes quite extensive—for example, in sickle cell disease.[4] MR angiography (MRA) allows the diagnosis of cerebrovascular disease non-invasively in many cases and may—for example, reveal the presence of moyamoya ("puff of smoke" in Japanese) collaterals associated with occlusion or severe stenosis in children presenting with transient ischaemic attacks, seizures, chorea, or intellectual deterioration. Therefore, the paediatrician needs to be familiar with the wider concept of "stroke, stroke-like episode, and cerebrovascular disease" when faced with a child with an acquired neurological deficit of whatever duration.

Aetiology

The important risk factors in adults, such as hypertension, diabetes, alcohol abuse, and smoking, do not appear frequently in children with stroke, although some possible risk factors (such as sleep disorders) might be common to both age groups. A large number of chronic paediatric conditions, including congenital heart disease and sickle cell disease, predispose to stroke,[5] although at least half those presenting with stroke have no previous medical history. Venous thrombosis (associated with cyanosis and polycythaemia) and embolus from the heart are common mechanisms in cardiac disease, but aneurysms and dissections have been described,[6] and moyamoya occurs in

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patients with arch anomalies, including coarctation of the aorta, and in a number of syndromes (such as Down's and Williams's syndromes), which suggests than there might be a more generalised vasculopathy in some of these patients. The pathology in sickle cell disease is usually large vessel disease, which commonly presents as hemiparesis, but children with seizures or headaches should have venous thrombosis excluded.

In previously well children, a history of trauma, however minor, or infection, may suggest arterial disease such as dissection or stenosis; the latter has been described with varicella zoster and human immunodeficiency virus as well as with meningitis. Intrathecal production of antibodies to varicella zoster has been demonstrated in children with stroke and cerebrovascular disease up to four years after the primary infection.[7] Acute and chronic infections appear to be an important trigger in children[8] and young adults[9]; tonsillitis has long been considered a possible association and dental infection might also play a role. *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Helicobacter pylori*, and haemolysing streptococcus are specific pathogens, but a wide variety of bacteria and viruses have been implicated. Sudden onset may indicate an embolic origin, usually presumed to be cardiogenic in childhood, whereas a slowly evolving or stuttering neurological deficit suggests thrombosis and therefore cerebrovascular disease as the most likely underlying pathology. Such clinical clues to stroke syndromes and subtypes have been worked out in adults,[10] but can probably be transferred to paediatric populations.[11]Table 1 lists the common conditions predisposing to stroke in children.

Clinical presentation

Most children who have suffered a stroke present with a hemiparesis, sometimes accompanied by hemisensory signs or visual field defects. Gaze palsy or head turning suggests a large supratentorial infarct.[12] If headache is present, arterial dissection[13] or venous thrombosis[14] should be considered; migraine is common and although stroke may occur in adults, this is a rare association in the young[15] and other causes must be excluded. Seizures, with or without an associated focal neurological deficit, are a common presentation of cerebral venous thrombosis, particularly in neonates.[14] A deterioration in the level of consciousness is common in cerebral haemorrhage,[16] large middle cerebral territory infarcts,[12] and posterior fossa strokes,[17] and is an indication for immediate transfer to an intensive care unit with paediatric neurology and neurosurgery available.

Table 1 Common conditions predisposing to stroke

Condition	*Main pathologies*
Ischaemic stroke	
Congenital/acquired heart disease	Embolus, cerebrovascular disease (for example, dissection)
Sickle cell disease	Large vessel stenosis and occlusion
Trauma	Large vessel dissection
Dehydration	Venous sinus thrombosis
Meningitis	Basal vessel inflammation/spasm, stenosis, occlusion
Varicella	Large vessel stenosis
Acquired immunodeficiency syndrome	Large vessel stenosis
Haemolytic uraemic syndrome	Large vessel vasculitis
Homocystinuria	Large vessel stenosis and occlusion
Williams's syndrome	Moyamoya
Down's syndrome	Moyamoya
Haemorrhagic stroke	
Idiopathic thrombocytopenic purpura	Platelet count < $10–15 \times 10^9$/l
Haemophilia and other coagulopathies	Prolonged coagulation

Investigation

More than 80% of children presenting with ischaemic stroke have cerebrovascular disease,[18] which may change with time.[19] In the past, this needed to be demonstrated by invasive angiography, but the increasing sensitivity of magnetic resonance angiography (MRA)[20] and transcranial Doppler ultrasound[21] means that large vessel disease can be diagnosed acutely using these techniques; the latter technique is non-invasive and may be used as a screening technique in "at risk" populations, such as those with sickle cell disease.[21] Because carotid dissection is now diagnosable by MRI and angiography in most cases,[22] there is a good case for urgent MRI in young patients, but the radiologist should be informed of this possibility so that the appropriate sequences (T1 weighted spin echo with fat saturation and three dimensional "time of flight" or phase contrast MRA) are obtained; similar consideration should be given to the exclusion of venous thrombosis (MRI venography). MRI is therefore the preliminary investigation of choice, but where this is not available, CT to exclude haemorrhage is mandatory. After an interval, conventional angiography is usually required to exclude arteriovenous malformation or aneurysm in cerebral haemorrhage, unless there is an obvious clotting derangement, and may be needed in ischaemic stroke to resolve diagnostic issues, particularly if the MRA is normal or equivocal, so that small vessel disease (such as isolated cerebral angiitis)[23] can be excluded. The current advice is to proceed to conventional angiography in ischaemic stroke if the MRA is normal or equivocal or if there is evidence for moyamoya and surgery is planned[24]; there might be a higher diagnostic rate if angiography is performed soon after the stroke, but this may need to be balanced against the benefit of delaying—for example, to exclude important prothrombotic disorders. Families should be counselled that there is a 1% chance of stroke, although the risk may be lower in centres with a lot of experience and patients who do not have a stenosis.

The diagnostic rate for conventional echocardiography is disappointingly low but there is considerable evidence from the young adult population that otherwise unimportant cardiac anomalies, particularly patent foramen ovale, are associated with stroke; the roles of transoesophageal echocardiography[25] and contrast transcranial Doppler sonography[26] in demonstrating right to left shunt at atrial level have not yet been defined in childhood stroke. It is important to exclude cervical instability if the distribution of infarction is compatible with posterior circulation disease.[17] Most paediatricians investigating a child with stroke would

undertake a prothrombotic screen. In fact, the prevalence of previously described inherited prothrombotic disorders, such as protein C and S deficiencies, is probably not higher than that in the background population,[27 28] except perhaps for the factor V Leiden mutation, although acute abnormalties are common and may be important pathogenetically. There appears to be a high prevalence of an acquired antiphospholipid syndrome in childhood[29] as well as in adult stroke, although the importance of finding abnormally high anticardiolipin antibodies has not yet been fully worked out. The role of other abnormalities that appear to be risk factors for stroke in adults, such as the prothrombin 20210 polymorphism,[30] the von Willibrand factor,[31] and increased Lp(a) lipoprotein,[32] requires investigation. Hyperhomocysteinaemia,[33] which in adults appears to be related to a common thermolabile polymorphism in the 5,10-methylene tetrahydofolate reductase gene,[34] is particularly important because the risk of vascular disease may be reduced by vitamin B complex supplementation.[35] Iron deficiency might also be an important association in children with and without cardiac disease.[36 37] Appendix 1 gives an outline of apprpriate investigations for the diagnosis of stroke in children.

Treatment of acute stroke

In adults, the main focus of recent studies has been in looking at the possibility of minimising the effect of the initial stroke, using either thrombolysis or neuroprotection. One benefit of the trials has been an increased awareness of the need for rapid assessment and appropriate management of people with acute stroke. The concept of a "brain attack" has received widespread publicity in the USA and there is little doubt that stroke units save adult lives[38] and improve outcome in survivors.[39] One controlled study of intravenous tissue plasminogen activator (t-PA), conducted in adults who could be randomised within three hours, showed significant benefit in terms of outcome at three months.[40] However, thrombolysis in adults carries a 10% risk of haemorrhage, associated with considerable mortality, and the results beyond a three to six hour time window have been very disappointing.[41] Although children with a stroke often present to a doctor within three hours, because of the rarity of stroke, the low sensitivity of CT for diagnosing acute infarction, and the wide differential in this age group, the diagnosis is rarely made with any degree of certainty at this stage. In addition, mortality is lower 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 t-PA in this age group at the present time, although it may occasionally be justified in children known to be at risk (for example, because of congenital heart disease) who suffer a stroke in hospital. Infarct volume and outcome appear to be related to body temperature during the first few days after the stroke[42]; a direct causative effect remains unproven, but maintaining body temperature just below 37°C is unlikely to do harm.[43] Apart from preventing fever, there is no neuroprotective strategy available at the present time that could be recommended for use in children.

Nevertheless, there are a number of management strategies for individual patient groups that might make a difference,[44] in addition to the need for clot removal in haemorrhage. Seizures in the acute phase should be managed appropriately, although there is no evidence for a detrimental effect on outcome in adults. There is a case for surgical decompression in children presenting in coma with large ischaemic middle cerebral infarcts, which are almost always fatal if managed conservatively.[12] In children with sickle cell disease, exchange transfusion is recommended acutely, although this must be conducted slowly and with caution, in view of the association with neurological deterioration. The question of anticoagulation remains a difficult one. One large trial in adults suggested benefit,[45] whereas others have shown increased morbidity and mortality.[46] Despite the risk of haemorrhage, there are patient groups—for example, those with vessel dissection, venous sinus thrombosis,[47] and known prothrombotic abnormalities[29]—who should probably be anticoagulated acutely to prevent early recurrence. Aspirin appeared to be associated with a modest improvement in outcome, probably because of a reduction in early recurrence and perhaps also because of its antipyretic effect, in two very large controlled trials in adults,[46 48] and the risk of haemorrhage appears to be lower than with anticoagulants,[46] although further studies in children will be needed in view of the additional risk of Reye's syndrome. Appendix 2 gives details of appropriate management strategies for stroke in children.

Prevention of recurrence

There is much evidence for a large risk of recurrence of haemorrhagic stroke if arteriovenous malformations and aneurysms are left untreated. For untreated aneurysms, about 50% bleed again over the first month, whereas for arteriovenous malformations, there is a lifelong 2–3%/year risk of re-bleeding. Aneurysms are rare in childhood and a surgical opinion should be sought urgently. The options for arteriovenous malformations include surgery, stereotactic radiotherapy, and interventional neuroradiology.[49] Some lesions might not be treatable by all three methods but there is no controlled data available yet to guide management for those that are treatable. The best approach is probably to seek advice from an experienced team with access to the alternatives. Haematological advice should be sought for those with coagulopathies.

For ischaemic stroke, long term recurrence prevention is a controversial issue. B complex vitamin supplementation is probably reasonable in those with hyperhomocysteinaemia, although more research is required. There is considerable uncertainty over the appropriate dosage and duration of aspirin treatment in adults[50] and, again, the question of the risk of Reye's syndrome is important in children. The

Appendix 1
Investigation of aetiology

Neuroimaging of brain and vessels
- Magnetic resonance imaging (MRI) and MR angiography (MRA) to:
  - Exclude haemorrhage
  - Define extent and territory of infarct
  - Define vascular anatomy of circle of Willis and neck vessels
  - T1 weighted spin echo with fat saturation sequence to exclude dissection
- Computed tomography (CT) scan to exclude haemorrhage if MR not available acutely
- Conventional angiography if haemorrhage without coagulopathy or MRA normal

For those with haemorrhage
- Basic coagulation studies and platelets
- Conventional angiography if no bleeding diasthesis

For those with no infarct
- Electroencephalogram (unihemispheric slowing in hemiplegic migraine)

For those with an infarct in a vascular distribution and/or cerebrovascular disease
- Precordial echocardiography
  - Consider transoesophageal if normal (?same general anaesthetic as arteriogram)
  - Consider transcranial Doppler ultrasound with bubble contrast
- Blood tests (4 ml EDTA, 6–8 ml citrated, 2 ml heparinised, 5 ml clotted)
  - Full blood count, differential white cell count, and erythrocyte sedimentation rate
  - Iron, folate, red cell folate, and haemoglobin electrophoresis if appropriate ethnic group
  - Protein S (total and free)*, and protein C*
  - Antithrombin III*, heparin cofactor II*, plasminogen*, von Willibrand factor antigen, factor VIII*, factor XII*,and lupus anticoagulant
  - Anticardiolipin antibodies*
  - Factor V Leiden and activated protein C resistance
  - Prothrombin 20210 gene
  - Total homocysteine* (+ thermolabile methylene tetrahydrofolate reductase gene, serum folate, B6, and B12)
  - Fasting cholesterol and triglycerides and Lp(a) lipoprotein
  - Infection screen, including *Mycoplasma*, *Chlamydia*, *Helicobacter*, and *Borrelia* titres, and aspartate aminotransferase
- Serum and cerebrospinal fluid to look for intrathecal production of antibodies to varicella zoster
- Sleep study

For those with infarction in the territory supplied by the vertebrobasilar system (in addition)
- *x* Ray cervical spine in flexion and extension

For those with infarction not in a typical vascular distribution
- Cerebrospinal fluid lactate
- Plasma ammonia and amino acids
- Urine organic acids

*If performed acutely, must be repeated after 3 months.

Appendix 2
Management

Acute management
- Keep temperature between 36.5°C and 37°C
- Treat acute seizures

For haemorrhagic stroke
- Immediate referral to a centre with neurosurgical facilities (?for drainage)

For cerebellar stroke presenting in coma
- Referral to a centre with neurosurgical facilities (?for drainage hydrocephalus or decompression)

For large middle cerebral artery territory lesions presenting in coma
- Referral to a centre with neurosurgical facilities (?for decompression)

For stroke in sickle cell disease
- Exchange transfusion

For ischaemic stroke occurring in hospital and imaged within three hours
- Consider intravenous tissue plasminogen activator

For venous sinus thrombosis, extracranial arterial dissection, and known prothrombotic disorder
- Heparin acutely
- Warfarin for three to six months

For strokes secondary to other mechanisms
- Early prophylaxis with low dose aspirin (1 mg/kg)

For all
- Early rehabilitation by team comprising nursing staff, physiotherapist, occupational therapist, speech therapist, and psychologist

Prevention of recurrence

For sickle cell disease
- Regular transfusion (4–6 weekly) to keep haemoglobin S < 20%

For moyamoya
- Consider revascularisation, particularly if transient ischaemic attacks or cognitive decline

For homozygotes for the thermolabile methylene tetrahydrofolate reductase gene
- B complex vitamin supplementation

For those with an important prothrombotic disorder or extracranial arterial dissection
- Consider warfarin (discuss with haematologist in individual case)

For others with stroke in a vascular distribution and/or cerebrovascular disease
- Low dose aspirin 1 mg/kg

lifelong recurrence risk has not been defined for children, but because cerebrovascular disease is often found on follow up MRA, a low dose regimen (about 1 mg/kg) is probably justified. The relative risk of further stroke and life threatening haemorrhage on long term warfarin has not been assessed for patients with inherited thrombophilias, such as factor V Leiden, but there is a case for cautious anticoagulation in some patients, particularly if there are ongoing symptoms. Similarly, although patent foramen ovale may be closed at catheterisation, the long term risk/benefit ratio is impossible to determine at present. Patients with moyamoya often benefit from direct and indirect revascularisation,[51] in terms of cognitive as well as motor improvement. This may also apply to some patients with sickle cell disease, for whom the present recommendation of long term transfusion remains unsatisfactory because of the inevitable iron overload and the difficulties in ensuring adequate chelation. Nevertheless, until further evidence is available, children with sickle cell disease who have had a stroke or who have been found on screening with transcranial Doppler ultrasound to have intracranial velocities > 200 cm/second should be transfused long term to achieve a haemoglobin S < 20%, because there is considerable evidence that this is an effective method of ensuring primary as well as secondary prevention.[52] Appendix 2 outlines suggestions for the prevention of stroke recurrence in children.

Key messages
- Children presenting with a focal neurological deficit and any depression of consciousness should be referred urgently to a unit with neurosurgical facilities
- Most children presenting with stroke have cerebrovascular disease demonstrable with appropriate neuroimaging (magnetic resonance or conventional angiography)
- Sickle cell disease is one of the most common causes of stroke in childhood, but there may be no clinical manifestations; screening with transcranial Doppler ultrasound may detect large vessel disease in this at risk population
- Certain patient groups might require specific acute treatment or prophylaxis, although appropriately designed controlled trials are required

Conclusion
In summary, the recent advances in diagnostic techniques, particularly MRA, appear to have substantially decreased the proportion of completely idiopathic stroke, but the cause of the cerebrovascular lesions remains obscure in most patients. As more becomes known about the aetiology of stroke, management may be planned more logically, probably on an individual basis for the foreseeable future, although international multicentre controlled trials should be planned once tightly defined questions have been identified. Although there are no paediatric stroke units at present, because appropriate acute management almost certainly benefits some children, there is now a good case for early referral to centres with MRI available on call or at least for seeking advice on investigation and management as soon as

possible. As treatment for "brain attack" becomes feasible, advances in information technology might allow patients to receive treatment before they arrive in stroke units. To define the service needs, population based studies of incidence, aetiology, recurrence risk, and outcome of childhood stroke, stroke-like episodes, and cerebrovascular disease are needed. Collaborative research on an international scale will be required to improve outcome.

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