Stroke in children

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BACKGROUND
Stroke is a major cause of disability and death in children. It can have devastating consequences for families and enormous costs to society. Although considered rare, stroke is more common in children than brain tumours. Ten percent of children suffering stroke will die as a result, and at least 50% of survivors are left with significant neurological disabilities, learning difficulties or seizures.

OBJECTIVE
This article discusses risk factors, investigation, management and outcomes of ischaemic and haemorrhagic stroke in neonates and children.

DISCUSSION
Arteriopathies and cardiac disease are the commonest risk factors for childhood arterial ischaemic stroke (AIS). The cause of perinatal AIS is poorly understood, despite affecting 1 in 4000 newborns. Sinovenous thrombosis is commonly associated with head and neck infections, and haemorrhagic stroke with arterio-venous malformations. Magnetic resonance imaging is the diagnostic investigation of choice. Treatment recommendations are extrapolated from adults due to a lack of prospective interventional studies.

Although considered rare by adult standards, childhood stroke is more common than brain tumours and is among the top 10 causes of death in childhood.[1] Subtypes include:

- **arterial ischaemic stroke (AIS)**
- **cerebral sinovenous thrombosis, and**
- **haemorrhagic stroke.**

Mode of presentation, risk factors, aetiology, recurrence rates and outcomes are dependent on stroke subtype and the age of the patient. Brain imaging is required to confirm the diagnosis and to differentiate stroke from other paroxysmal neurological disorders.

Recognition that risk factors such as hypertension, smoking, and diabetes cause stroke through atherosclerosis has allowed development of evidence based therapeutic strategies in adults. In comparison there is limited understanding about risk factors, aetiology, treatment and predictors of outcome of childhood stroke. Systematic coordinated care and research are only now being initiated.

Arterial ischaemic stroke

Arterial ischaemic stroke has an estimated incidence of 2.7 per 100 000 children per year with 25–30% of all cases occurring in neonates and approximately 50% occurring in children less than 1 year of age; 20–40% of children have recurrent strokes.[2]

Case vignette 1
Baby SV was born to a primiparous mother who had an uncomplicated pregnancy followed by spontaneous onset of labour at term. There was meconium stained liquor and fetal decelerations during labour so she proceeded to an emergency caesarian section. The infant had seizures on the first day of life, associated with apnoea and focal clonic jerking and was loaded with phenobarbitone. Frequent clinically silent focal seizures were captured on electroencephalogram (EEG), arising from the left parietal region. Magnetic resonance imaging within 48 hours of birth showed an acute infarct in the left middle cerebral artery territory (*Figure 1*).

Perinatal stroke

Perinatal AIS is defined as a fetal or neonatal cerebrovascular event. It is 17 times more common than stroke in later childhood and has an estimated incidence of 1 in 4000 live births.[3] This approximates the frequency of stroke in the fourth and fifth decades of life.[4] Perinatal stroke has a low recurrence rate, estimated at 3–5%.

The cause of perinatal stroke is usually unknown. Maternal risk factors include pre-eclampsia, oligohydramnios,

prolonged rupture of the membranes and chorioamnionitis. Neonatal risk factors include birth trauma, cardiac and other congenital abnormalities (see *Case vignette 1*).[3,5] Thrombophilic disorders have been reported in 25–68% of cases.[6] Stroke may be diagnosed in the neonatal period in the setting of encephalopathy but many cases have a delayed presentation[7] with early hand preference in later infancy due to emerging hemiparesis (see *Case vignette 2*) Likely pathogenic mechanisms include changes in the coagulation system leading to thrombosis of intracranial vessels or embolism from the heart, umbilical vessels or the fetal side of the placenta. This combined with the presence of right to left cardiopulmonary communication through persistent fetal connections such as the foramen ovale and ductus arteriosus allow clots to travel directly to the brain.[7]

Case vignette 2

LH, an infant aged 11 months, presented with delayed acquisition of motor milestones. His parents noted a strong left hand preference with the child crossing the midline to reach for toys if placed out of his reach on the right side. Examination revealed fisting of the right hand. MRI subsequently showed an established left middle cerebral artery infarct with cystic cavitation and gliosis (*Figure 2*).

Childhood AIS (age >1 month)

Risk factors for childhood AIS are age dependent (*Table 1*). Arteriopathies are a major cause of arterial stroke, accounting for around 50% of cases.[8] Transient cerebral arteriopathy is the most common nonprogressive angiopathy and there is often a history of chickenpox infection in the 12 month period preceding the stroke.[9] (See the article by Jukes this issue). Magnetic resonance imaging (MRI) characteristically shows a focal or segmental stenosis of the distal internal carotid artery (ICA) or proximal segment of the middle cerebral artery (MCA) with a subcortical infarct (*Figure 3, 4*). Children can have recurrent strokes up to 8 months following presentation, however the arteriopathy either regresses or stabilises within 2 years.[10]

Cardiac disease accounts for up to 25% of cases.[11,12] Congenital cyanotic or complex congenital heart defects are the most common causes, particularly when there is a right to left shunt or polycythaemia. Prothrombotic abnormalities have been identified in 38% of children with acute stroke,[13] but other authors have not found a causal relationship,[14,15] and therefore their role in paediatric stroke is still not established.

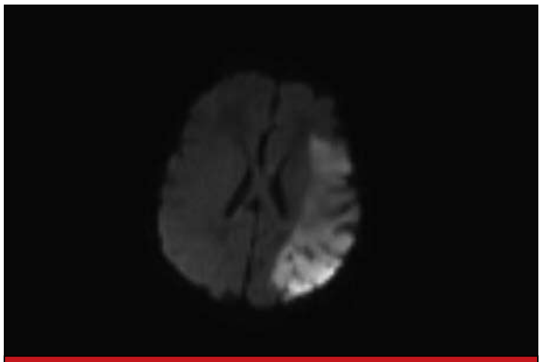

Figure 1. Diffusion weighted imaging showing a cytotoxic oedema due to an acute cerebral infarct in the left middle cerebral artery

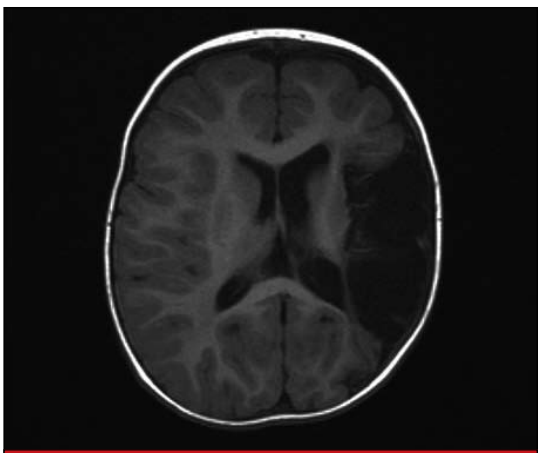

Figure 2. Axial T1 weighted MRI showing established left middle cerebral infarct with cystic encephalomalacia and gliosis in an infant with a congenital hemiplegia

Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVST) is less common than AIS with an estimated incidence of 0.67 per 100 000 population per year. Once again, age distribution is skewed with infants less than 1 year of age comprising half the cases. Neonatal CSVT has an estimated incidence of 41 per 100 000 population per year.[16] Thrombosis more often involves the superficial venous system and can be associated with venous infarction in 40–50% of cases. Intraventricular haemorrhage can also be seen in around 33% of newborns.[17]

Risk factors for childhood CSVT include dehydration, local head and neck or systemic infections, congenital heart disease and anaemia. Additional risk factors for neonatal CSVT include asphyxia, chorioamnionitis, congenital heart disease, polycythaemia, sepsis and dehydration.[17] Thrombophilia defects have been reported in childhood and neonates but their role has not been well defined.[18]

Haemorrhagic stroke

Haemorrhagic stroke (HS) is as common as AIS with an estimated incidence of 1.5–2.9 per 100 000 population per year. The most common presenting symptoms are headache or vomiting due to raised intracranial pressure, seizures and focal neurological deficits. Arteriovenous malformations (AVMs) and fistulae are the most common causes of HS and are associated with a 2–4% risk of re-bleeding per year.[19] Other causes of HS include haematological disorders, coagulopathies, trauma, brain tumours, cavernomas and, rarely aneurysms.[5]

Clinical symptoms

Clinical symptoms are summarised in *Table 2*. Symptoms such as focal motor, sensory, visual or speech deficits in children should not be attributed to other paroxysmal disorders such as migraine if there is no prior history of complicated attacks or to a postictal Todd paresis (localised weakness after a seizure) in the absence of a known diagnosis of focal epilepsy.

Specifically ask about:

- recent head/neck injury, chiropractic neck manipulation
- varicella infection in the past 12 months
- migraine
- oral contraceptive pill or illicit drug use (in adolescents)
- family history of early onset (<age 55 years) stroke, heart attack, deep vein thrombosis or pulmonary embolus.

General examination should include auscultation for cardiac murmurs, carotid or cranial bruits and measurement of blood pressure.

Investigations

In contrast to adult patients presenting with stroke symptoms who are investigated promptly with urgent neuroimaging, the diagnosis of stroke in children is often delayed.[20] Acute neurological deficits are frequently attributed to other problems such as migraine, encephalitis, tumours and postictal Todd paralysis following seizures, contributing to the delay in diagnosis.[20]

Imaging

- Urgent neuroimaging is the cornerstone of diagnosis. In older children noncontrast computerised tomography (CT) scan of the head should be performed to determine if haemorrhage is present
- MRI with diffusion weighted sequence should be performed within 48 hours of presentation to detect cytotoxic oedema
- For AIS and CSVT imaging of the intracranial and neck vessels should be performed, using CT or MRI techniques
- In neonates, cranial ultrasound is not sensitive enough to detect infarction and MRI with diffusion weighted imaging and magnetic resonance angiography (MRA) of the intracranial and neck vessels is recommended.

Other investigations

- Electrocardiogram (ECG) and echocardiogram with bubble (agitated saline) study and Valsalva manoeuvre to look for patent foramen ovale and paradoxical right to left embolisation
- Full blood count, basic biochemistry and coagulation screen (PT, APTT, INR)

Table 1. Causes of childhood arterial ischaemic stroke (1 month – 18 years)

Arteriopathies
- Acute transient vasculopathies including postvaricella angiopathy
- Moyamoya disease
- Sickle cell disease
- Arterial dissection
- Primary central nervous system angiitis
- Fibromuscular dysplasia
- Systemic vasculidities including lupus, and polyarteritis nodosa, Wegener granulomatosis
- Postirradiation

Cardioembolic stroke
- Congenital heart disease
- Acquired heart disease cardiomyopathy, rheumatic heart disease, endocarditis

Thrombophilias
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Factor V Leiden mutation
- Prothrombin 20210A mutation
- Antiphospholipid syndrome

Inborn errors of metabolism
- Mitochondrial cytopathies (MELAS)
- Homocystinuria
- Fabry disease
- Congenital glycosylation disorders

Other
- Migrainous infarction
- Bacterial meningitis
- Hypertension

- Prothrombotic work up (preferably before commencement of anticoagulant therapy) including antithrombin deficiency, protein C, protein S, plasminogen, activated protein C resistance (APCR), factor V Leiden, prothrombin 20210A gene mutation, anticardiolipin antibody (ACLA), lupus anticoagulant, and serum homocysteine levels
- In perinatal stroke, prothrombotic studies should be deferred until the infant is older than 6 months of age and both parents should be screened to enable counselling about risk to future pregnancies.

Management

General measures

- Simple measures such as correction of fever, maintenance of normal blood glucose, blood pressure and aggressive treatment of seizures have been shown to improve outcome in adults.
- Oxygen supplementation as required to keep SaO2 >95% through first 24 hours poststroke
- Load with intravenous phenytoin or alternatively phenobarbitone in neonates if seizures occur
- Children should have an evaluation of swallowing as soon as possible following admission. Attention to feeding, communication and pain are also important
- Early liaison with rehabilitation professionals should be initiated once the child is stable.

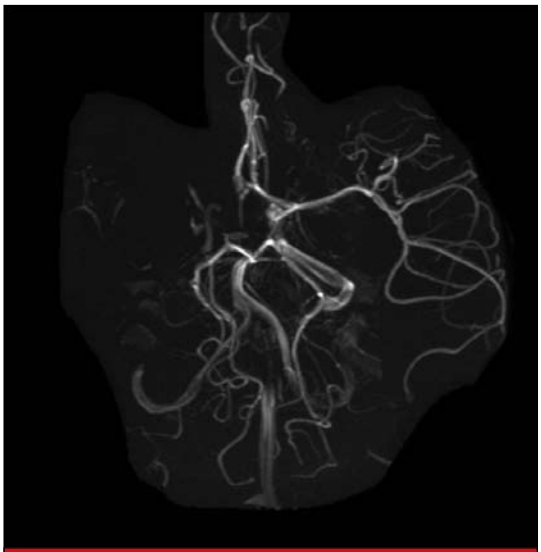

Figure 3. MRA showing a flow void at the trifurcation of the right distal internal carotid into the middle, anterior cerebral and posterior communicating arteries

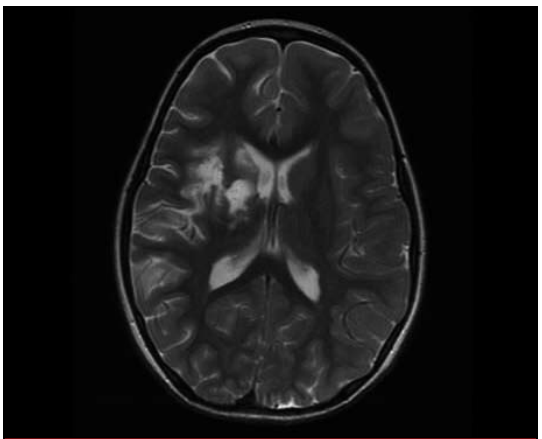

Figure 4. Axial MRI image showing subcortical right middle cerebral artery stroke secondary to postvaricella angiopathy

Acute interventions

Delay in diagnosis is the major obstacle to acute thrombolytic therapies in children. Mean times from symptom onset to presentation to any health professional have been documented at 34.5 hours with time to imaging 42 hours.[21] Tissue plasminogen activator (tPA) trials in the stroke population have excluded any individuals under 18 years of age and therefore the evidence for efficacy and safety of tPA in children is lacking.

Secondary prevention

There are no randomised controlled secondary prevention trials so treatment recommendations are extrapolated from adults. This may not be appropriate due to maturational differences in coagulation and vascular systems as well as different stroke mechanisms as outlined above. Treatment options include antiplatelet and anticoagulant agents. Guidelines for acute thrombophilic management,[6] and for diagnosis, management and rehabilitation[22] have recently been published. They are however, largely based on consensus opinion due to the limited evidence base for acute interventions in this population (*Table 3*).

Rehabilitation

Early liaison with rehabilitation professionals is indicated to enable prompt intervention and to ensure smooth transition for the child and their family from the hospital setting to the community. Rehabilitation professionals will address not only the motor and cognitive impairments arising directly from the stroke, but also external factors such as education of the family, school and local services.

Outcomes

Contrary to traditional views, it is now accepted that children don't necessarily recover better than adults, and may in fact have more debilitating impairments that interfere with normal development and lifestyle. Long term neurological deficits occur in 50–85% of children with AIS and epilepsy occurs in 15–20% of survivors.[2] A 10% mortality has

been reported in neonates with AIS and two-thirds have neurological deficits.[23] Motor sequelae in neonates and older children are most commonly spastic and/or dystonic hemiplegia, with hand function most affected.[24–26] Experience suggests that the clinical presentation may evolve over a matter of months to years, particularly in children with dystonia. The outcome of childhood sinovenous thrombosis is somewhat better, however 38% had neurological deficits and 15% had seizures in one series.[18] Neurological sequelae are uncommon in neonates.[27]

Although estimates vary, recent studies have found at least half of children who have a stroke have neuropsychological impairments, particularly affecting verbal learning, memory and processing speed difficulties.[28,29] Unlike in adult stroke, these impairments are less predictable according to lesion location. Factors such as age at stroke, co-existence of other stroke risk factors and seizures at onset may also influence the presence of impairments. Speech, and behaviour or learning problems have been described in around 50% of cases.[30,31]

There is limited information on the functional impact of childhood stroke. However, one study has shown mild to moderate activity limitations affecting motor function, self care and educational abilities following middle cerebral artery territory stroke, and that parent social and emotional health is also affected.[26]

Assessment of children with stroke should take into account the child's age at the time of stroke and premorbid neurodevelopmental function. Age appropriate instruments should be used where possible to assess cognitive, motor, sensory, behavioural and speech ability following stroke.[22] The extent and nature of deficits may not be apparent poststroke, but may emerge in the long term, as children face increasing academic, physical and social challenges. This highlights the need for paediatric rehabilitation intervention and long term multidisciplinary follow up.[22]

Community support

A parent support group 'Strokidz' (www.strokidz.com) has recently formed to provide support and advocacy for children and families affected by childhood stroke. Improvement in the content and distribution of appropriate information to parents is a major area of interest for this group.

Future directions

Research into childhood stroke has been complicated by small population numbers, differences in practice, and paucity of stroke specific assessment tools. Priorities for research include the identification of risk factors, reliable markers and clinical signs for early detection; measurement of longitudinal recovery; and the impact of acute medical and rehabilitation interventions. These questions will only be answered through multicentre collaboration.

The Royal Children's Hospital in Melbourne is one of 77 institutions contributing to the International Pediatric Stroke Study (IPSS), a prospective registry that has collected epidemiological data on over 1200 children with stroke since 2003 (www.sickkids.on.ca/cstrokestudy). This large prospective study will be important in improving our understanding of childhood stroke and providing opportunities for interventional trials to establish dosage guidelines, efficacy and safety of acute thrombolytic therapy and the most appropriate secondary prevention treatments. Further development of paediatric stroke programs and multicentre international collaborations also required to improve evidence based practice in this group of children.

Table 2. Clinical features

Childhood AIS

- Sudden onset of focal motor, sensory, visual or speech deficits are the usual mode of presentation

Perinatal AIS

- Seizures, lethargy and apnoea are the commonest presenting problems in the neonatal period, however the stroke may go unrecognised because focal neurological signs are rarely evident
- Early hand preference and lateralised neurological deficits are typical modes of presentation in older infants with congenital hemiplegia

CSVT

- Signs and symptoms are often nonspecific, including headache, altered consciousness and papilloedema, however seizures are also common
- Seizures, irritability and lethargy are the most frequent presenting signs in newborns

Table 3. Secondary prevention

Childhood AIS

- Initially aspirin 1–5 mg/kg/day, unfractionated or low molecular weight heparin while being investigated for cardioembolic sources and vascular dissection
- Continue low molecular weight heparin or warfarin for 3–6 months if dissection or cardioembolic source is confirmed
- Continue aspirin, 1–5 mg/kg/day for all other children for a minimum of 5 years

Neonatal AIS

- Aspirin or anticoagulation 6–12 weeks for cardioembolic AIS
- Anticoagulation or aspirin for noncardioembolic AIS are not recommended unless there are recurrent events

Children and neonatal CSVT without significant intracranial haemorrhage

- Anticoagulation for 3 months aiming for a target INR between 2.0–3.0

Children and neonatal CSVT with significant intracranial haemorrhage

- Radiological monitoring and anticoagulation if clot propagation occurs

Summary of important points

- Stroke is more common than brain tumour and is among the top 10 causes of death in childhood.
- 25% of all paediatric stroke occurs in neonates under 4 weeks of age and almost 50% in children less than 1 year of age.
- Risk factors include pregnancy and birth complications, thrombophilias and cardiac problems.
- Stroke should be suspected in children with sudden onset of weakness, speech or visual disturbance and in term neonates with encephalopathy or seizures.
- 20–40% of children with a diagnosis of stroke will have recurrent strokes.
- It has been shown that transient vasculopathy can occur weeks to months following varicella infection.
- Sinovenous thrombosis should be suspected in neonates with unexplained seizures, irritability or increasing head circumference and in older children with headache/papilloedema, unexplained acute encephalopathy or neurological deficits.
- 50–85% of childhood stroke survivors will be left with long term problems including seizures, motor, behaviour, social, speech or learning difficulties, emphasising the need for access to multidisciplinary rehabilitation and ongoing developmental surveillance.

Conflict of interest: none declared.

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