

PAEDIATRIC STROKE

In spite of better diagnosis of paediatric stroke, its management remains challenging.

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Improved clinical recognition and advances in neuro-imaging techniques have enabled greater recognition of stroke in the paediatric population. However, management remains challenging because of the diversity of the underlying aetiologies, range of risk factors and lack of standard treatment guidelines for children. The World Health Organization definition of stroke is 'a clinical syndrome of rapidly developing focal or global disturbance of brain function lasting >24 hours, or leading to death with no obvious nonvascular cause'. This definition may not always apply to paediatric strokes because children may present with transient signs and previous illnesses, especially infections such as varicella zoster, which do not preclude the diagnosis of strokes in this population.

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Estimates of annual incidence from population-based studies range from 2.5 to 13 per 100 000 children per year.^{1,2} The Canadian Pediatric Ischemic Stroke Registry yielded an incidence of 3.3 cases per 100 000 children per year, of which 80% were arterial ischaemic stroke (AIS).³ In the newborn period the incidence of ischaemic strokes is estimated to be about 1 per 4 000 live births.⁴ The incidence of childhood cerebrovenous sinus thrombosis is 0.3 per 100 000 children per year, and neonates make up 43% of these patients.⁵ There is a paucity of epidemiological data from Third-World settings.

Mimics of childhood stroke

Not all patients with focal neurological deficits have had a stroke. In a prospective paediatric cohort of 143 patients evaluated for suspected stroke, 30 had neurological deficits without cerebrovascular disease, two-thirds of whom had serious problems requiring comprehensive investigations.⁶ Examples of conditions that can mimic stroke are shown in Table I.

Classification

Strokes can be classified as either haemorrhagic or ischaemic arterial (Fig. 1) or venous (Fig. 2), and if arterial, can be embolic or thrombotic. About half of all childhood strokes are haemorrhagic.

Underlying vascular lesions (e.g. arteriovenous malformations (AVMs)) and intravascular factors are the most common causes of haemorrhagic strokes (Table II).⁷

Stroke occurs across all ages. In paediatric patients two major age groups are identified because of differences in risk factors involved, pathophysiological, clinical presentation, therapeutic and prognostic implications, i.e. neonatal stroke and childhood stroke.

Table I. Mimics of childhood stroke⁶

- Seizures and epilepsy (Todd's paresis)
- Migraine
- Psychogenic
- Posterior reversible leukoencephalopathy syndrome
- Inflammatory disease (post-infectious)
- Intracranial infection
- Metabolic stroke

Table II. Causes of haemorrhagic stroke

Vascular	Intravascular
Congenital vascular anomalies	Haematological disorders
AVMs	Immune thrombocytopenic purpura
Venous angioma	Thrombotic thrombocytopenic purpura
Cavernous malformation	Haemophilic states
Intracranial aneurysm	Factor deficiencies
	Liver dysfunction
	Vit K deficiency
Vasculopathies	
Moyamoya	
Connective tissue disorders	
Sickle cell disease	

Neonatal stroke

The newborn period confers the highest risk period for childhood ischaemic stroke. Focal patterns of ischaemic brain injury to the perinatal brain are increasingly recognised. This has facilitated improved identification of risk factors and management.

The recently revised definition of perinatal ischaemic stroke is 'a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolisation, between 20 weeks of fetal life through to the 28th postnatal day, and confirmed by neuroimaging or neuropathological studies'.⁸

Not all patients with focal neurological deficits have had a stroke.

Multiple sub-classifications of neonatal strokes are proposed.^{8,9} The clinically relevant neonatal stroke syndromes are:⁹

- arterial ischaemic strokes (AIs)
- cerebral venous sinus thrombosis (CVST)
- peri-ventricular venous infarction.

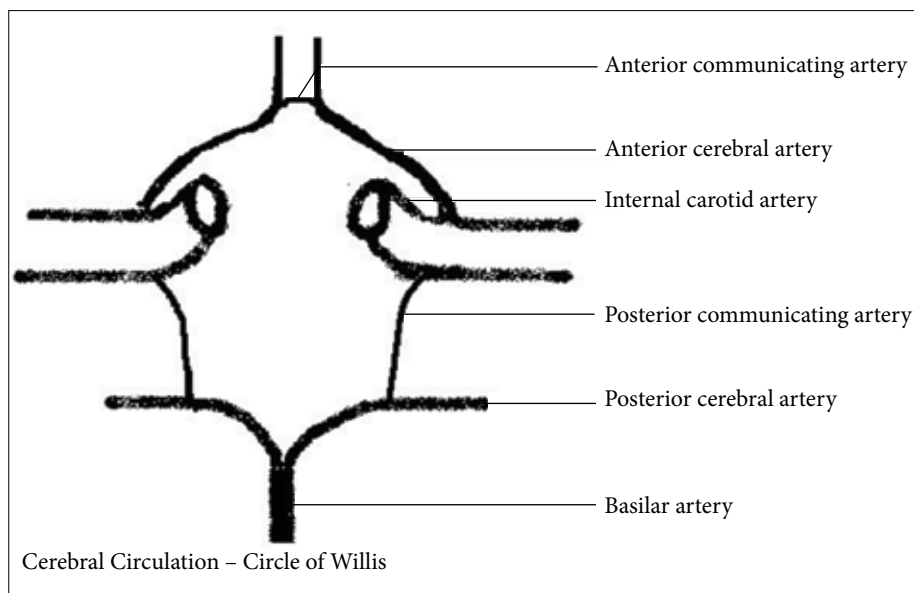


Fig. 1. Cerebral arterial supply.

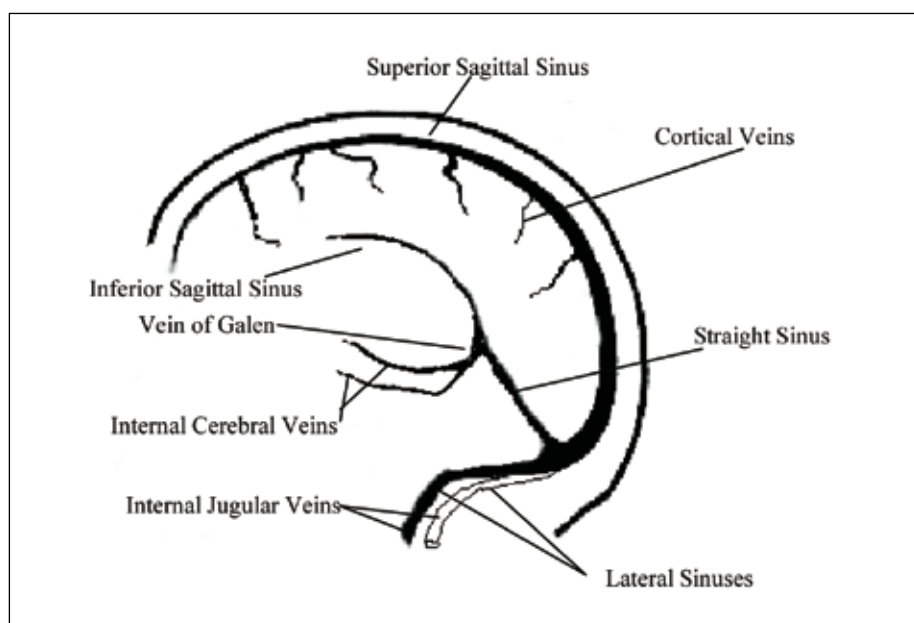


Fig. 2. Cerebral venous drainage.

Table III. Perinatal stroke risk factors

Maternal	Placental
Autoimmune	Placental thrombosis
Coagulation disorders	Fetomaternal haemorrhage
Twin to twin transfusion	Abruption
Drug abuse (e.g. cocaine)	Chorioamnionitis
Infection	

Clinical features of strokes in the neonatal period are nonspecific; most neonates commonly present with focal seizures. Strokes account for about 10% of neonatal seizures. In AIS, seizures often occur in the absence of neonatal encephalopathy or focal deficits.¹⁰ CVST may present with signs of more diffuse neurological dysfunction. Peri-ventricular venous infarction following germinal matrix haemorrhage occurs in the pre-term population. In most infants the diagnosis is only made during the first

year of life when the child presents with developmental delay, epilepsy or preferential hand use in infancy.

Neonates share risk factors for strokes with older children. However, there are some unique risk factors for strokes in this period (Table III).

With few acute clinical signs and frequent retrospective recognition, the diagnosis of perinatal stroke is primarily by neuro-

imaging. Cranial ultrasound can diagnose neonatal stroke but the sensitivity and specificity are low.¹¹ Computed tomography can confirm arterial ischaemic stroke and cerebral venous sinus thrombosis. Magnetic resonance imaging is the investigation of choice in perinatal stroke.

About half of all childhood strokes are haemorrhagic.

Management of neonatal stroke

Neuro-protective strategies used for global ischaemic neonatal brain injury are potentially applicable to stroke.¹² Supportive measures as in childhood stroke (see below) are beneficial.

Hypothermia is an established protective strategy in hypoxic brain injury and may be useful in neonatal strokes. Specific therapy would include correction of coagulopathies in patients with intra-cranial haemorrhage.¹⁴

Consensus guidelines recommend that anticoagulation therapy should be considered in neonates with severe thrombophilias, multiple cerebral or systemic emboli, or clinical or radiological evidence of propagating CVST despite supportive therapy.^{15,16}

Secondary stroke prevention is not recommended for other aetiologies.² Multidisciplinary rehabilitation is essential for all patients.

Outcome

Neonatal strokes are the commonest cause of congenital hemiplegic cerebral palsy. Motor deficits are the commonest long-term complication and occur in 30 - 60% of patients with arterial ischaemic stroke, 30 - 50% in cerebral sinovenous thrombosis and >80% in periventricular venous infarction. Epilepsy occurs in up to 60% of survivors.

The newborn period confers the highest risk period for childhood ischaemic stroke.

Childhood stroke

Risk factors

In contrast to adult stroke, which is usually secondary to atherosclerotic disease, arterial cerebrovascular disease in children is often a result of a combination of factors (Table IV). Risk factor frequency varies according to age and the population studied. Children are more likely to have an inflammatory or infectious cause for their stroke. In resource-poor settings such as South Africa, infections such as bacterial meningitis, tuberculous meningitis and HIV are probable risk factors. Cardiac diseases are a cause of childhood AIS in about a third of cases.¹⁷ Other risk

factors in the older child are haematological and prothrombotic conditions, post-varicella vasculopathy, moyamoya syndrome, and other vasculopathies.⁷

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Clinical presentation

Arterial ischaemic stroke

The valuation of a child with AIS starts with the history. This should include the following:

- onset – sudden onset suggests an embolic process; presence or absence of seizures; gradual onset suggests an arteriopathy or thrombotic occlusion
- recent illness – chickenpox in previous weeks or months (up to 1 year); recent head or neck trauma (arterial dissection)
- underlying medical conditions (as in Table II)
- family history of young stroke/thrombosis.

A full physical examination should be done and should include:

- Glasgow Coma Scale (GCS)
- signs of raised intracranial pressure
- signs of meningitis
- focal signs
- presence of aphasia/dysphasia
- evidence of a bleeding diathesis or vasculitis
- cardiovascular system examination.

The typical clinical presentation of AIS in toddlers and older children is an acute, prolonged neurological deficit such as hemiparesis, with or without seizures.^{7,15,17} Seizures at the onset of stroke are more frequent in younger children than in adults and as a result the diagnosis of stroke is not always considered until the child's 'Todd's paresis' does not resolve as expected. Clinical signs may be subtle in children under 1 year

of age, where seizures and encephalopathy are commoner than focal signs.

The anterior circulation, especially the middle cerebral artery (MCA), is generally the most commonly affected; hence the hemiparesis (Table V).¹⁷ Involvement of the posterior circulation is much rarer and many cases are associated with trauma and vertebrobasilar dissection or vascular malformations. Dystonia is also commoner in paediatric stroke patients with basal ganglia involvement.

Weakness is usually maximal immediately after onset with flaccidity predominating initially. Long tract signs evolve over time. Generally right-sided hemiparesis will be accompanied by dysphasia which tends to be mainly expressive in children under 8 -10 years of age.

Cerebral sinovenous thrombosis

- lethargy
- nausea
- vomiting
- headache
- seizures (focal, generalised)
- depressed level of consciousness (drowsiness, coma)
- hemiparesis or other focal neurology.

Investigations

The cause of stroke in certain children is clear from the beginning, for example in

those with a known cardiac disorder or sickle cell disease. Even in this group precipitating factors need to be looked for. Neuro-imaging guides the direction of investigations as well as their urgency.

Neonatal strokes are the commonest cause of congenital hemiplegic cerebral palsy.

Neuro-imaging of brain and vessels for arterial ischaemic stroke

- computed tomography (CT) scan to exclude haemorrhage and to define the extent and territory of the infarct (Fig. 3)
- magnetic resonance imaging (MRI) and MR angiography (MRA) (Figs 4 and 5) if available to exclude haemorrhage, define extent and territory of infarct, and define vascular anatomy of circle of Willis and neck vessels (MRA)
- T1-weighted spin echo with fat saturation sequence to exclude dissection
- conventional angiography if haemorrhage without coagulopathy or MRA is normal.

For those with haemorrhage

- basic coagulation studies and platelets
- conventional angiography if there is no bleeding diathesis.

Intravascular	Vascular	Embolic
Haematological	Vasculopathies	Congenital heart disease
Sickle cell	Focal cerebral arteriopathy (eg. post-varicella)	Complex CHD
Leukaemia	Moyamoya disease or syndrome	Acquired heart disease
Polycythaemia		Rheumatic HD
Prothrombotic states	Vasculitides	Infective endocarditis
<i>Congenital</i>	Meningitis	Prosthetic heart valves
Protein S, C deficiency	Childhood primary angiitis of the central nervous system (cPACNS)	
Factor V Leiden mutation	Takayasu's arteritis	
<i>Metabolic</i>	Cervical arterial dissection	
Homocysteinaemia		
Hyperlipidaemia		

Artery involved	Area of ischaemia	Clinical features
Internal carotid	Usually area of MCA or both MCA and ACA territories - may need key for all abbreviations	Hemiplegia; hemianopia; aphasia if dominant hemisphere
Middle cerebral artery (MCA)	Convexity of hemispheres; insula; part of temporal lobe; internal capsule and basal ganglia; orbital aspect of frontal lobe	Hemiplegia with upper limb predominance; hemianopia; aphasia if dominant hemisphere
Anterior cerebral artery (ACA)	Mesial aspects of hemispheres; paramedian part of convexity; anterior part of internal capsule and basal ganglia	Hemiplegia with lower limb predominance
Posterior cerebral artery (PCA)	Lower temporal lobe; posterior thalamus and subthalamic nuclei	Hemiparesis; ataxia; vertigo; homonymous hemianopia
Thalamostriate; penetrating branches	Caudate; putamen; internal capsule	Hemiplegia; motor sensory or mixed; no hemianopia; sometimes speech involvement

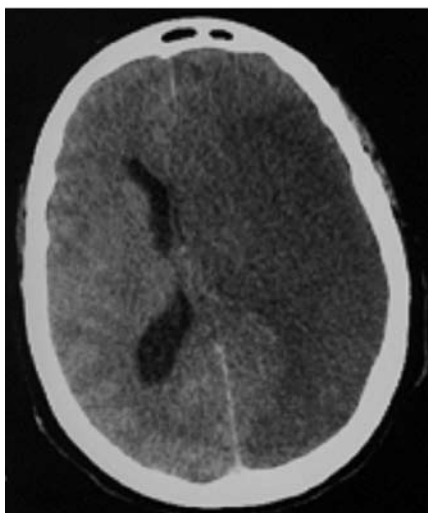


Fig. 3. Brain CT scan showing a large left MCA infarct.

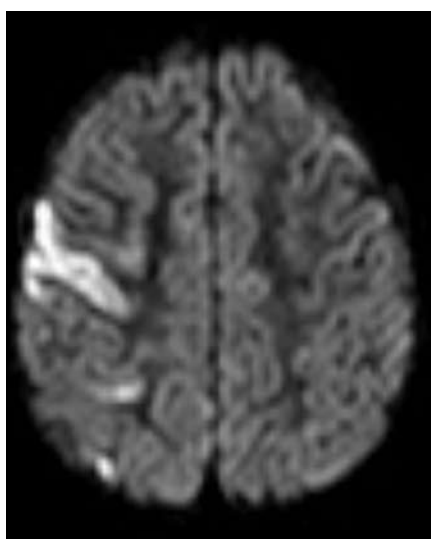


Fig. 4. MRI diffusion weighted image showing an MCA infarct.

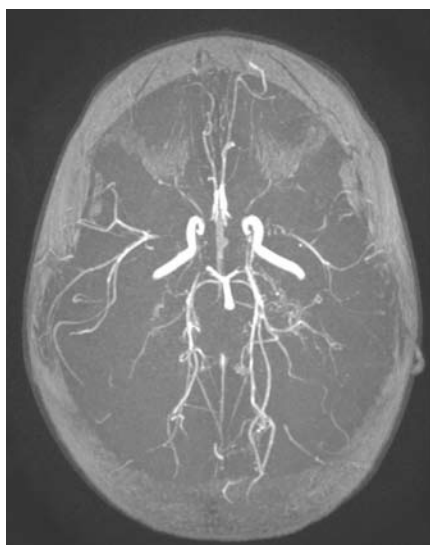


Fig. 5. MR angiogram showing moyamoya vasculopathy.

For those with an infarct in a vascular distribution and/or cerebrovascular disease

- precordial echocardiography
- consider transoesophageal if precordial

- echocardiography is normal
- carotid Doppler studies.

Children are more likely to have an inflammatory or infectious cause for their stroke.

Blood tests

- full blood count, differential white cell count, and erythrocyte sedimentation rate
- haemoglobin electrophoresis if appropriate ethnic group
- fasting cholesterol, triglycerides and lipoprotein (a)
- infection screens, including *Mycoplasma*, HIV, TB, varicella (extended work-up for HIV-positive patients), CMV, toxoplasmosis, lymphoma
- serum and cerebrospinal fluid to look for evidence of inflammation/infection and intrathecal production of antibodies to varicella zoster
- factor V Leiden
- prothrombin 20210 gene
- anticardiolipin antibodies and lupus anticoagulant
- total homocysteine + thermolabile methylene tetrahydrofolate reductase (MTHFR) gene if hyperhomocysteinaemia.

The following should be deferred for 3 months, as factors may be consumed in the acute phase

- protein S and protein C
- antithrombin III.

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.

Diagnosis of sinovenous thrombosis

- history of associated pre-existing disorder
- uncontrasted CT scan
- contrasted CT scan
- MRI with contrast
- diffusion-weighted imaging
- MR venography (depending on availability).

Management

The management of stroke in childhood is divided into acute management, prevention of recurrence, and early disability assessment and management.

Acute management

This entails acute supportive and neuroprotective care. It is also directed

at preserving the penumbra and involves maintaining the following:

- body temperature at low-to-normal (hyperthermia exacerbates brain ischaemia)
- euglycaemia
- adequate blood oxygenation
- adequate cerebral perfusion and management of raised ICP.

Treat acute seizures and reduce brain metabolic demand.

Children with haemorrhagic stroke should be referred immediately to a centre with neurosurgical expertise and facilities.

For large MCA infarcts with swelling and coma referral to a centre with intensive care and neurosurgical facilities is necessary, because the patient may need decompression.

In the case of sickle cell disease primary and secondary prevention is by prophylactic blood transfusion (to keep haemoglobin S below 30%) in children with high MCA velocities on transcutaneous Doppler studies. Acute treatment with exchange transfusion for stroke is necessary in sickle cell disease.¹⁷

Antithrombotic therapies¹⁵⁻¹⁷

Table V gives the international guidelines. In individual children the risks of recurrence or progression of cerebral thromboembolism should be balanced against the risks of treatment, especially haemorrhage. The treatment approaches used in children have been adapted from adult studies. The agents used include low molecular weight heparin, warfarin and aspirin. Recently there has been an increase in the use of anticoagulation in children, especially in cerebral sinovenous thrombosis.

Clinical signs may be subtle in children under 1 year of age, where seizures and encephalopathy are commoner than focal signs.

Recommendations^{16,17}

For secondary prevention in underlying cardiac disorders and vascular dissection anticoagulation with low molecular weight heparin should be used. These children should be managed in consultation with the relevant specialists, e.g. paediatric haematologist, cardiologist and neurologist.

Use low-dose aspirin at 1 - 5 mg/kg/day for children with arterial ischaemic stroke, for all patients with vasculopathy (including moyamoya disease/syndrome), for patients with unknown aetiology (NB: there is as yet no agreement on the duration of aspirin use - possibly as long as the vasculopathy persists).

Paediatric stroke

There is currently no place for thrombolytic agents in childhood stroke, and they should be regarded as dangerous.

Patients with moyamoya disease/syndrome should be referred to specialised neurosurgical units where indirect revascularisation procedures may be considered.

Rehabilitation

Rehabilitation should be multidisciplinary, including physiotherapy, occupational therapy, speech and language therapy.

It should address feeding and nutrition, communication, pain, mobility, positioning and handling requirements. Rehabilitation should start as soon as possible after the stroke and must involve caregivers.

Prognosis^{7,10,17}

- Mortality rate in childhood AIS is 0.09 per 100 000, with a case fatality rate of approximately 15%.
- Increased mortality is found in males and those with pre-existing critical illness.
- At least two-thirds of survivors have

residual neurological impairments (mostly sensorimotor deficits).

- Vision, speech, cognition and behaviour are also adversely affected.
- Recurrence rates of AIS vary from 6% to 41%, and are higher when there is an underlying cerebral arteriopathy.

References available at www.cmej.org.za

IN A NUTSHELL

- Stroke diagnosis is usually delayed in children.
- Multiple risk factors often exist and are different from those in adults.
- Infections play a major role in the aetiology of stroke in poorly resourced settings.
- Seizures are more common at presentation, especially in the young.
- Acute neuroprotective care is vital to minimise the size of the subsequent infarct and clinical severity.
- Evidence for treatment of paediatric stroke is needed; practice is currently based on adult evidence.
- Vasculopathy is a significant risk factor for the recurrence of childhood stroke.

SINGLE SUTURE

Amputation risk predicted using eye test

A glimpse in an eye might soon be enough to diagnose the nerve damage associated with diabetes.

Up to 50% of people with diabetes experience nerve damage, which, in extreme cases, leads to the loss of limb sensation, prompting the need for amputation.

Nerve fibre damage is typically assessed through invasive tests, including nerve and tissue biopsies. Now Nathan Efron and colleagues at the Queensland University of Technology in Brisbane, Australia, have developed a non-invasive alternative.

Diabetes affects peripheral nerves, and Efron suspected that it might also leave a signature in the cornea – the most densely innervated tissue in the body. He has now shown that this is true using a corneal confocal microscope: on average the corneas of diabetic people with nerve damage have a lower density of nerve fibres, and nerves are shorter than in healthy controls.

Efron's team has developed a clinical test based on the findings. Team member Rayaz Malik at the University of Manchester, UK, developed software that compares images of the central cornea with those taken from diabetics with varying degrees of nerve damage. According to Efron, the test is now being used by several hospitals worldwide.

New Scientist, 26 March 2011, p. 21.

SINGLE SUTURE

Drink like the French

Soaring rates of alcohol abuse and liver disease in the UK can be reversed by copying the French and Italian strategies of cutting cheap booze from supermarkets.

So say a group of researchers, whose analysis shows that since 1986 UK death rates from liver disease, 80% of which are alcohol related, have more than doubled from 4.9 to 11.4 per 100 000 people. In France and Italy, the opposite occurred, with death rates of 50 per 100 000 in the early 1960s falling to less than 10 per 100 000 today.

The solution, says lead author Nick Sheron at the University of Southampton, UK, was to take cheap alcohol out of the system. 'France has done the impossible, reducing liver death rates while increasing the value of its alcohol economy,' he says. 'The UK drinks industry needs to start selling quality, not quantity.'

New Scientist, 26 February 2011, p. 4.