

CHILDHOOD ARTERIAL ISCHEMIC STROKE: RISK FACTORS, MANAGEMENT AND OUTCOMES

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Pediatric Stroke:

The incidence of stroke in childhood likely ranges from 2.3 to 13 per 100,000 children,^{1,2} approximately half of which are arterial ischemic stroke.

Diagnosis:

Diagnosis of AIS in childhood is complicated by relative infrequency of stroke in children compared to adults, frequent mimics of childhood stroke, challenges in assessing neurologic deficit in young children, and the differential diagnosis (Table 1). Diagnosis therefore requires confirmatory neuroimaging.

Table 1. Differential Diagnosis of Acute Arterial Ischemic Stroke in children ^{3,4}
Transient ischemic attack
Hemorrhage
Seizure and Todd's paralysis
Encephalitis
Complicated Migraine
Psychogenic
Amnesic
Acute disseminated encephalomyelitis
Tumor
Methotrexate toxicity
Concussion
Non-accidental trauma

Approximately half of children presenting with acute arterial ischemic stroke will have a known risk factor such as congenital heart disease or sickle cell anemia. With extensive investigation including neurovascular imaging and thrombophilia studies, most children will have at least one risk factor identified (Table 2), however the significance of isolated risk factors is often unclear. Arterial ischemic stroke in childhood is likely a multifactorial disorder in any cases.

Table 2. Risk factors for arterial ischemic stroke in adults vs children	
Adults	Children
Hypertension	Cardiac
High cholesterol	Congenital heart disease
Diabetes	Acquired heart disease
Cigarette use	Cerebral arteriopathy
Obesity	Moyamoya
Cardiovascular disease	Chronic systemic disorder
Obstructive sleep apnea	Sickle cell anemia
Heavy ETOH use	Malignancy
Older age	Thrombophilia
	Acute systemic illness
	Chronic head and neck disorder
	Acute head and neck disorder
	Infection

Childhood arterial ischemic stroke may be more similar to young adults (≤ 45 years) than older adults, however when compared with young adults, stroke etiology in children is more likely to be "other" or

“multifactorial”, and children are more likely to have steno-occlusive arteriopathy or moyamoya, and less likely to have cervicocerebral artery dissection.⁵ Stroke severity, mortality and outcome is similar among children and young adults.⁵ Frequently identified risk factors in childhood arterial ischemic stroke include arteriopathy, congenital heart disease, sickle cell anemia, and inflammatory and infectious disorders:

- **Cerebral Arteriopathy:** Cerebral arteriopathy is present in almost half of children presenting with an initial stroke, and is a significant risk factor for initial as well as recurrent stroke.⁶⁻⁸ Commonly identified arteriopathies include focal cerebral arteriopathy, a discrete localized stenosis, and moyamoya. In addition, cervicocephalic arterial dissection (CCAD) accounts for 7.5% to 20% of childhood AIS.^{9,10} Among one series of 30 children, vertebral artery dissection accounted for half of posterior circulation strokes.¹¹ Arterial ischemic stroke can also be associated with primary and secondary CNS vasculitis involving large and medium arteries. Infection with wild-type varicella zoster virus is associated with vasculopathy and stroke, particularly within the first year following chicken pox.^{12,13} Cerebral arteriopathy may be heralded by transient ischemic attacks.¹⁴
- **Congenital/Acquired Heart Disease:** Almost one third of childhood arterial ischemic stroke is due to cardioembolic stroke, with the highest risk associated with complex congenital heart disease (CHD) and right-to-left shunts.⁷ Stroke can occur during cardiac surgery or catheterization but can also occur without apparent trigger. Recurrent stroke occurs within 10 years in one-quarter of children.¹⁵ The significance of the role of patent foramen ovale in childhood stroke is not established, and paradoxical embolism through as PFO as a cause of stroke in childhood remains a diagnosis of exclusion.¹⁶
- **Sickle cell anemia:** Without preventative treatment, 11% of children will have a stroke by age 20.¹⁷ This risk is markedly decreased by the use of chronic red blood cell transfusions in children with elevated transcranial Doppler (TCD) velocity in the middle cerebral artery.^{18,19} Stroke in sickle cell anemia is often associated with cerebral arteriopathy.²⁰⁻²²
- **Hypercoagulable States:** Protein S deficiency, protein C deficiency, factor V Leiden mutation, antithrombin III deficiency, elevated lipoprotein(a), homocystinuria and antiphospholipid antibodies are associated with AIS in childhood.²³ The risk is increased when there are multiple thrombophilias or other risk factors present.
- **Infection:** In addition to varicella, bacterial, mycotic and tuberculous meningitis are associated with childhood arterial ischemic stroke. Infection in general also increases the risk of childhood stroke.²⁴
- **Inflammatory/Autoimmune:** Primary and secondary inflammatory disorders are associated with childhood arterial ischemic stroke, particularly due to arteriopathy.

Management:

Management of stroke in childhood is complicated by the high frequency of co-morbid conditions, which may be a risk factor or cause of the stroke, and frequently complicated treatment. Reperfusion therapies such as IV tPA and endovascular thrombectomy are increasingly used in children, although are not FDA approved in childhood, and safety and efficacy data is lacking.^{25,26} Treatment strategies are primarily directed at limiting injury (rescuing the penumbra) and preventing early recurrence (Table 3). There are published guidelines for the use of antithrombotic medications for the secondary prevention of stroke in childhood.^{25,26}

Supportive	Specific Intervention
<u>Adequate perfusion</u>	<u>Aspirin</u>
Bedrest/Head of bed flat	<u>Anticoagulation</u>
Permissive HTN	Cervical artery dissection
<u>Oxygen</u> if hypoxic	Cardiac thrombus
Supplemental oxygen in sickle cell anemia	Severe thrombophilia
<u>Fever:</u>	<u>Steroids</u>
Prevent/treat fever	Vasculitis
<u>Seizures:</u>	<u>Anti-viral</u>
Treat seizures	Varicella vasculopathy
Prophylactic AED not indicated	<u>Transfusion</u>
<u>Surgical decompression:</u>	Sickle cell anemia
Decompressive hemicraniectomy	Anemia
Suboccipital craniectomy	Surgical revascularization in moyamoya

Follow-up:

Most children will have neurologic deficit following stroke, many requiring inpatient rehabilitation medicine care. Educational assessments and neuropsychological testing will facilitate return to school. Children and families also benefit from ongoing support and often formal counseling as they adjust to the sequelae of childhood stroke.

Resources for acute care:

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- Wainwright MS, Grimason M, Goldstein J, Smith CM, Amlie-Lefond C, Revivo G, Noah ZL, Harris ZL, Epstein LG. Building a pediatric neurocritical care program: a multidisciplinary approach to clinical practice and education from the intensive care unit to the outpatient clinic. *Semin Pediatr Neurol* 2014; 21: 248-254.

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