

# Ischaemic Stroke in Children - Overview Including an Asian Perspective

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## Abstract

Stroke is an important cause of death and disability in children. Although uncommon in children compared to adults, childhood stroke is less rare than previously thought. Improved understanding and advances in neuroimaging techniques have resulted in improved recognition and diagnosis of this disorder. Multiple causes and risk factors contribute to the etiology of stroke in children. The current review will provide an overview of recent advances in our understanding of childhood stroke and its implications during this period of life. In particular, this article will review the available data from Asian countries.

## Background

For the clinician, the diagnosis of ischaemic stroke in children is a challenge. Stroke is uncommon in children and is therefore rarely considered as the first diagnosis when a child presents with the symptoms. In children, the presentation is varied; subtle and non-specific that can be attributed to other neurological disorders such as focal seizure, Todd's paresis, complicated migraine and intracranial haemorrhage, demyelination and tumours. As a result the diagnosis of ischaemic stroke is often missed or delayed. Multiple causative and risk factors contribute to

the etiology of stroke in children, which differ significantly from those in adults.<sup>1</sup> The consequence is lifelong disability of a significant proportion in the affected children.<sup>2</sup> Several therapeutic interventions including thrombolytic and neuroprotective therapies have proved to be effective in adults with ischaemic stroke, however, to be effective and safe, these interventions must be instituted within a narrow therapeutic window (typically within 3-6 hours from symptom onset).<sup>3-5</sup> In children, since disability from stroke will impact the individual and society for many decades over their life span compared to adults, the development of beneficial hyper-acute therapies is of even greater importance, necessitating prompt and correct stroke diagnosis.

Although systematic approaches to paediatric stroke care and research are underway, these are still at very early stages. In paediatric stroke, randomized controlled studies are lacking and the available literature is only limited to case series and population based studies. The majority of paediatric stroke data is reported from North America and Europe, largest being the recently completed Canadian Paediatric Ischaemic Stroke Registry(CPISR). Except few population studies, data from developing countries largely comprises of case reports and series.

This article reviews various classifications, subtypes and clinical presentation of paediatric stroke including data from the CPISR. It mainly focuses on the recent advances and developments in our understanding of causative and risk factors, investigations, treatment and outcomes of children with ischaemic stroke, with particular emphasis on the available data from Asian countries.

## Definitions, Classification and Subtypes

Stroke is classified into: ischaemic stroke, resulting from vascular occlusion, and haemorrhagic stroke, resulting from vascular rupture.

### Paediatric Ischaemic Stroke

Paediatric stroke is categorized into childhood stroke (occurring between 1-month and 18-years of age) and perinatal stroke (occurring in-utero to 1-month of age). The perinatal stroke is categorized as acute neonatal (occurring between birth to 1-month of age) and prenatal stroke (occurring in-utero) and has been discussed in detail in a separate article in the same issue.

The ischaemic stroke subtypes include: arterial ischaemic stroke(AIS), caused by occlusion or stenosis of the cerebral arteries, and cerebral sinovenous thrombosis(CSVT), caused by occlusion of the cerebral veins or venous sinuses.

### Arterial Ischaemic Stroke

Arterial ischaemic stroke is defined by the presence of persistent focal neurological deficit of acute onset, and in infants, seizures alone or other signs of encephalopathy e.g. extreme irritability or altered consciousness, and/or neuroimaging evidence of focal parenchymal infarct or infarcts conforming to corresponding known arterial territory (Figure 1).

In some children, focal neurological deficits are transient, lasting less than 24-hours. When there is no

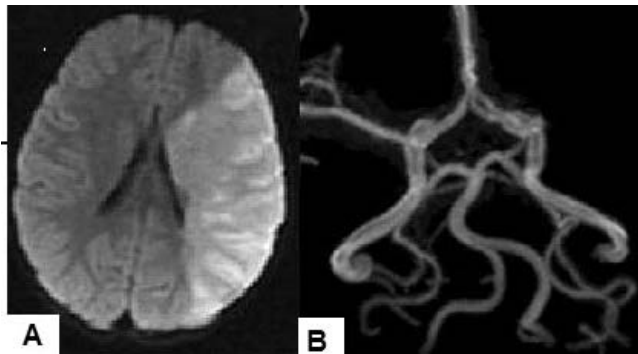


Figure 1. Two year old boy with complete left middle cerebral artery territory cardioembolic stroke secondary to atrial myxoma. A) Axial diffusion weighted MRI brain demonstrating diffusion restriction in left frontal and parietal regions, with involvement of both cortical and sub-cortical structures. B) Time of flight MR angiogram revealing left middle cerebral artery complete occlusion at its origin.

neuroimaging evidence of new focal area(s) of infarction and the event is not due to other etiologies (e.g. seizure, migraine) the event is defined as transient ischemic attack(TIA).

## Epidemiology

The reported incidence of childhood AIS, based on population studies and hospital discharge data bases, ranges from 0.6 to 7.9 per 100,000 children per year.<sup>6</sup> Over recent years, several studies including the CPISR have reported an increase in the overall average annual incidence of AIS in children.<sup>6,7</sup> In the CPISR, an incidence of AIS was estimated as 1.5 per 100,000 children per year with 25% occurring in newborns (10.2 per 100,000 live births per year in newborns).<sup>7</sup> Over half of the strokes occur in children less than one year of age.

Only two Asian studies have reported population based incidences among Asians. One study was based in Hong Kong and another in an Iranian province. The Hong Kong study included both ischaemic and haemorrhagic stroke and estimated an incidence of 2.1 per 100,000 children per year.<sup>8</sup> The Iranian study reported an incidence of 1.8 per 100,000 children per year.<sup>9</sup> Over half of the stroke occurred in children less than 36-months. A population based study in the United States also investigated the incidence of stroke among Asian American children and reported similar incidence rates (1.9 cases per 100,000 person years).<sup>10</sup> Based on these population based studies, the incidence of stroke among Asian children is likely to be within the range of 1.9 to 2.1 per 100,000 children per year (Table1).

Table 1. Annual Stroke Incidence In Asian Countries.

Studies	Annual Incidence*	Haemorrhagic Stroke	Ischaemic Stroke		Total Stroke Cases
			AIS	CSV	
Hong Kong <sup>8</sup>	2.1	14	36	36	50
Iran <sup>9</sup>	1.8	-	17	17	17
Al-Khobar Saudi Arabia <sup>11</sup>	29.7 <sup>+</sup>	3	28	28	31
Riyadh Saudi Arabia <sup>12</sup>	27.1 <sup>+</sup>	19	79	79	104

\*Cases per 100,000 children population per year, +Based on hospital admission database.

Studies based on hospital discharge databases have found higher incidences.<sup>6,10,11</sup> In the United States, a national study of hospital discharge codes for ischaemic stroke for children, revealed an estimated incidence of 7.8 per 100,000 children per year.<sup>6</sup> In Asia, studies based on hospital admission database have estimated comparatively higher incidences, ranging from 27.1 to 29.7 per 100,000

children per year.<sup>11,12</sup> These studies were reported from two large hospitals in Saudi Arabia. The reason for the increased incidence is likely related to the fact that both hospitals serve as tertiary care centers and provide services to several regions of the country.

### Clinical Presentation

The clinical presentation of AIS is age related and often non-specific in children. Due to the infrequent occurrence of stroke in children, the symptoms of AIS are often attributed to other neurological disorders that are commonly seen in children, such as seizures with ictal or post-ictal Todd's paresis, complicated migraine, intracranial tumor, infection or demyelination.

In infants and young children, AIS usually presents with seizures, irritability or altered consciousness. Hemiparesis although not uncommon, is difficult to recognize in this age group. Older children typically present with focal neurological deficit usually hemiparesis and/or

facial droop with or without seizures.<sup>2</sup> They can also present with other neurological deficits such as speech, visual, focal sensory or coordination abnormalities. Compared to adults, seizures, fever, lethargy and headache are frequent in children with AIS. The presentation also differs based on the location of infarction determined by the vascular territory and circulation involved.

In the CPISR, 69% children with AIS presented with focal neurological deficits and 37% with seizures. The focal deficits included motor deficits 78%, speech abnormalities 16%, visual deficits 10% and other deficits 32%.<sup>7</sup> Data from Asian countries has also revealed similar figures.<sup>8,9,12-17</sup>

Although the majority of childhood AIS present with single episode of focal neurological deficit, preceding TIAs are present in about one third. In children with TIAs, prompt evaluation with neuroimaging is important to rule out AIS and to initiate preventative antithrombotic treatment without delay.

**Table 2. Characteristics of Children with Ischaemic Stroke Reported from Asian Countries.**

Characteristics (in percentage)	Pakistan <sup>14</sup> (N=37)#	India <sup>13</sup> (N=43)	Iran <sup>9</sup> (N=17)	Saudi Arabia <sup>12</sup> (N=104)	Turkey <sup>19</sup> (N=57)	Thailand <sup>16</sup> (N=35)	Hong Kong <sup>8</sup> (N=36)**	China <sup>15</sup> (N=157)
<b>Demographics</b>								
Age at stroke*	NA(0.16-14)	8(1-16)	5.5(0.7-4.9)	2.2(1-12)	2.4(NA)	NA(0.5-15)	5.6(NA)	NA(0.3-16)
Male Sex	53.6	39.5	58.8	54	49	NA	56	58.6
<b>Clinical Features</b>								
Hemiparesis	100	86	100	67.3	68.4	69	34	81.5
Monoparesis	-	-	-	-	-	-	-	2.6
Speech abnormalities	-	23	17.6	21	-	9	10	15.9
Visual abnormalities	-	-	-	-	-	3	12	-
Altered consciousness	-	11	-	16.3	8.7	54	30	5.7
Seizures	-	27	47	47.1	19.2	43	52	20.4
Other <sup>+</sup>	-	34	35.2	60.6	-	37	30	14.6
<b>Radiological Features</b>								
Anterior circulation	-	100	88.3	-	-	-	52.7	71.3
Posterior circulation	-	-	11.7	-	-	-	5.5	3.1
Multiple territories	-	-	-	-	-	-	41.6	25.4
<b>Etiology/Risk factors</b>								
Cardioembolic	10.8	-	11.8	5.8	24.5	17	41.6	-
Arteriopathy	-	32.5	-	14.4	12.2	17	30.5	8.9
Intracranial trauma	-	-	11.8	2.9	-	-	-	10.8
Intracranial infection	62	-	23.5	15.4	-	-	13.8	12.1
Prothrombotic disorder	-	-	5.9	34.6	10.5	5.7	0	1.27
Haematological disorder	-	-	-	37.5	3.5	3	13.8	1.27
Other <sup>++</sup>	8	4.6	23.5	6.7	26	5.7	5.5	42.6
Idiopathic	8.9	23	23.5	10.6	40.3	43	8.3	32.5

\*Mean (range) in years, NA: Not available or not reported in the study, +Include headache, dizziness, vomiting and fever, ++Including dehydration, non-specific head and neck infection and other acute systemic illnesses, #37 children with ischaemic stroke, \*\*Demographic and clinical features include children with haemorrhagic stroke.

## Aetiologies and Risk factors

The aetiologies and risk factors of childhood AIS are multiple.<sup>2</sup> Contrary to adults in whom atherosclerosis is the leading cause of AIS, congenital cardiac disease, arteriopathies, infection and prothrombotic and haematological disorders are the commonly identified risk factors for paediatric AIS. At least half of the children with AIS have no prior significant medical history.<sup>18</sup> In addition, multiple risk factors often coexist in an individual child with AIS. The identification of associated etiologies or risk factors is important since these are closely linked to the recurrence risk and poor outcomes in children with AIS.

In childhood AIS, the reported frequency of potential etiologies and risk factors vary considerably depending upon the population studied and extent of etiological investigations. Several studies from North America and Europe have identified risk factors in 70 to 90% in children with AIS.<sup>7,18</sup> In Asia, an etiology was identified in over 50% of children with AIS.<sup>8,9,12,14-16,19</sup>

In the CPISR, etiologies and risk factors included: cardiac disease 29%, arteriopathy 69%, head and neck pathology (infections, trauma) 31%, prothrombotic disorders 22% and acute systemic illness 26%.<sup>7</sup> In Asia, except few studies that reported an increased frequency of intracranial infections<sup>9,14,20</sup>, the commonest etiology was cardioembolic stroke.

Common aetiologies and risk factors causing AIS in children are briefly discussed below. The results from Asian countries are summarized in Table 2.

### Cardiac Diseases

Cardioembolic stroke, one of the most common etiologies for AIS identified in children, was present in 20 to 28 % of children.<sup>1,7-9,12,14-16,18-20</sup> In children, congenital malformations with intracardiac shunting, cardiomyopathies, arrhythmias and endocarditis are predominant aetiologies. The majority of cardioembolic AIS occur in the setting of surgery or diagnostic and interventional catheterization, with highest risk in the first few years of life.<sup>18</sup>

### Arteriopathies of Childhood

The term arteriopathy or vasculopathy is collectively used to describe disorders of the cerebral arterial abnormalities that predispose to AIS. Recent studies report presence of an arteriopathy in about 30% to 60% of children with AIS.<sup>7,18,21</sup> Childhood arteriopathies can be either self limited and monophasic or have a relentlessly progressive course.<sup>21</sup> Common arteriopathies in children with AIS include arterial dissection, moyamoya, inflammatory, infectious and post infectious arteriopathy and diffuse vasculitis involving the central nervous system (CNS).

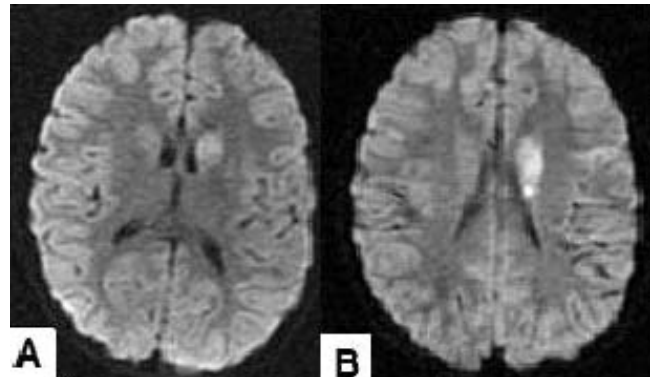


Figure 2. Eight year old girl with left basal ganglia stroke secondary to post varicella angiopathy. A and B) Diffusion weighted MRI brain images demonstrating diffusion restriction involving the head and body of the caudate nucleus on the left.

Arterial dissection results from a tear to the arterial wall often related to trauma but can occur spontaneously in children.<sup>22</sup> Moyamoya disease is a progressive vasculopathy characterized by stenosis of the distal internal carotid arteries and formation of arterial collateral vessels. Examples of inflammatory arteriopathies include transient cerebral arteriopathy of childhood, isolated angiitis of the CNS and CNS vasculitis associated with systemic inflammatory disorders. Inflammatory arteriopathies that occur after infection are termed post infectious, for example post-varicella angiopathy<sup>21</sup> (Figure 2).

### Infections

There is a strong relationship between infections and stroke in children. Most commonly associated infections with childhood stroke include meningitis, encephalitis and septicemia. An increased frequency of intracranial infections, up to 56%, has been reported from Asian countries especially in children younger than 5-years.<sup>9,14,20</sup>

### Prothrombotic and Haematological Disorders

Prothrombotic or coagulation disorders have been identified in about 18-68% of children with AIS.<sup>18,23</sup> The wide variation in the reported occurrence of prothrombotic abnormalities across studies is due to geographic and ethnic disparities and nature and extent of investigations. Most common prothrombotic abnormalities include deficiencies of Protein C, Protein S, antithrombin III and plasminogen, serum elevations of lipoprotein(a), homocysteine and antiphospholipid antibodies and factor V Leiden, prothrombin 20210A gene and methyltetrahydrofolate reductase mutations.

Sickle cell disease (SCD) is the most common haematological disorder associated with paediatric AIS, particularly in Asia. About 25% of patients with homozygous SCD develop AIS either due to acute sickle crises or a vasculopathy, often moyamoya. Other

haematological disorders associated with childhood AIS include iron-deficiency anaemia, polycythaemia and thrombocytosis.<sup>18,23</sup>

### Other Risk factors

Other risk factors are similar to adult AIS and include personal history of migraine, use of oral contraceptives, drug abuse (amphetamines, cocaine), metabolic and lipid disorders.<sup>2</sup> Genetic predisposition to stroke, a speculated association/cause, is currently being investigated.<sup>24</sup>

### Diagnosis

The diagnosis of AIS in children is based on both clinical suspicion of stroke and its differentiation from other conditions that mimic its presentation. The confirmation requires early and specific neuroimaging.

Head CT scan is often the first neuroimaging test done for parenchymal imaging in both children and adults because of its potential to readily rule out haemorrhage and easy accessibility and applicability. However, CT scan may miss the signs of early infarction, especially when done within 12 hours. If available, MRI with diffusion weighted sequences is more sensitive and specific neuroimaging modality for acute infarction. In children, MRI has become the preferred modality due to the rarity of stroke and existence of broad differential diagnoses that are more common than stroke.

In suspected AIS cases, non-invasive vascular imaging (CT or MR angiography) should be performed as part of the initial study since the detection of an arteriopathic condition may guide initial treatment. In selected cases, conventional cerebral angiography may be required acutely when initial non-invasive vascular imaging suggests vascular occlusion or is inconclusive. Once the AIS diagnosis is confirmed, an aggressive search for the underlying etiology and risk factors is recommended since treatment, prognosis and outcome of AIS are largely dependent on the associated conditions, which may themselves require urgent treatment.

### Treatment

Major challenges in the treatment of acute childhood AIS is related to stroke recognition and prompt diagnosis. In children, recent literature indicates significant delay to AIS diagnosis, with median interval from symptom onset to diagnosis ranging from 22.7 to 35.7-hours and delay to initial neuroimaging over 8-hours.<sup>25,26</sup>

In contrast to adults, there are no multicenter or randomized controlled clinical trials in children to establish evidence based guidelines for acute treatment or prevention

of childhood AIS. The treatment is mainly extrapolated from the adult studies or based on paediatric case series and reports. Systematic approaches for the management of childhood AIS and consensus guidelines are just beginning to appear.<sup>27,28</sup>

In adults, over the past decade, the use of fibrinolytics ("clot busting" agents) has become the main focus for AIS treatment. Fibrinolytic therapy with tissue plasminogen activator (tPA) is the currently approved hyperacute therapy shown to significantly reduce disability from AIS in adults. In the National Institutes of Neurological Disorders and Stroke trial, patients who received tPA were 30% more likely to have minimal or no disability 3-months after treatment, compared to placebo.<sup>5</sup> However, there is significant risk of haemorrhage especially when tPA is instituted after therapeutic window (3-hours for intravenous and 6-hours for intra-arterial). Several other experimental clot lysing therapies and interventions and neuroprotective strategies such as whole body hypothermia or selective head cooling have either shown promising results or are currently being tested in adults.<sup>3,4,29</sup>

In children, although case reports on the use of both intravenous and intra-arterial tPA have been published<sup>15,30</sup>, the safety and efficacy has not been tested. This combined with significant maturational and developmental differences between children and adults, pose important ethical and practical challenges for the application of above listed therapies in children. Major international collaborations are underway to investigate these hyperacute therapies in paediatric AIS.

Most important and strongly recommended, in both children and adults, are urgent general supportive strategies that decrease the volume of infarction by salvaging the penumbra (the surrounding ischemic viable brain tissue at risk of permanent infarction). These include maintenance of adequate cerebral blood flow, normoglycaemia and hydration, and aggressive treatment of fever and seizures.<sup>2</sup>

After the initial hyperacute therapeutic window, secondary prevention therapy with an antiplatelet agent is recommended in almost all adult AIS patients. Exceptions are patients with dissection and cardioembolic stroke, when antithrombotic therapy with anticoagulants is advised. The secondary prevention therapies for adult AIS has been shown to reduce risk of recurrence and hence improve outcome<sup>31</sup>. Although there is no evidence for secondary prevention therapies in childhood AIS, similar treatment approaches are recommended based on adult safety and efficacy data and 15%-25% risk of recurrence with childhood AIS.

Two recent guidelines for secondary prevention in children with AIS have recommended early antithrombotic

therapy (within 12-hours of stroke symptoms), particularly for conditions that increase the immediate risk of recurrent stroke such as cardioembolic stroke and arterial dissection.<sup>27,28</sup> According to the Australian AIS treatment guideline, for children with confirmed AIS without haemorrhage, standard unfractionated or low molecular weight heparin is recommended in the first 5 to 7 days until the evaluation for underlying etiologies and risk factors is completed. In situations where the coagulation system plays a major role such as cardio-embolic stroke, arterial dissection and prothrombotic disorders, children are continued on either oral or subcutaneous anticoagulants for 3-6 months and then switched to an antiplatelet agent, usually aspirin. All others are treated with aspirin.<sup>27,28</sup>

## Outcome

In children with AIS, permanent motor or cognitive disabilities have been reported in over 60% and death in 5%-28%.<sup>17,32,33</sup> Most frequently reported residual neurological deficit is hemiparesis. Others include speech, cognitive and behavioural deficits. Long term sequelae including headache, epilepsy or movement disorders are also reported in 15%-30% of children with AIS.<sup>7,32</sup> Decreased quality of life reportedly occurs in over 50% of survivors of childhood AIS, which affects not just the individual but the entire family and the community at large.<sup>34</sup> Recurrent AIS or TIAs are reported in 20%-35% of children with AIS.<sup>1,7</sup>

The indicators of poor motor and cognitive outcome in children with AIS include young age at the time of stroke, presentation with altered consciousness or seizures, cortical or complete middle cerebral artery territory infarction, infarct size and identification of certain prothrombotic abnormalities.<sup>33</sup> In children with AIS, the outcome is also dependent on the presence or absence of associated conditions.<sup>1</sup>

## Cerebral Sinovenous thrombosis

Cerebral sinovenous thrombosis is defined by the presence of thrombus or flow interruption within cerebral veins or dural venous sinuses with or without evidence of venous infraction. Haemorrhage, parenchymal and intraventricular, may be present in about 30% of children with CSVT.<sup>35</sup> A clinical presentation characteristic of CSVT includes headache, altered consciousness, seizures, and focal or diffuse neurologic deficits.

Compared to AIS, CSVT is less common in children. The CPISR estimated an incidence of 0.67 per 100,000 children per year, with over 40% occurring in newborns.<sup>35</sup> Data from Asian countries is limited (Table1).

Various risk factors that contribute to the etiology of

childhood CSVT include intracranial and systemic infections, cranial trauma, dehydration, chronic systemic diseases, prothrombotic disorders, congenital heart disease and iron-deficiency anaemia.

The diagnosis of CSVT requires neuroimaging evidence of thrombus or lack of flow in the cerebral veins or venous sinuses either by head CT venogram or MR venogram.

As with AIS, the treatment of CSVT includes both general supportive measures and antithrombotic therapy. In addition, treatment of underlying etiology is extremely important such as treatment of infections and dehydration. The antithrombotic therapy is aimed at preventing the clot propagation and recurrence within the cerebral venous system. For children without evidence of significant intracranial haemorrhage, anticoagulation for 3-6 months is recommended, with reassessment of re-canalization at 3-months. With significant intracranial haemorrhage, monitoring with serial neuroimaging is advised. In case of clot propagation, treatment with anticoagulation is advised.<sup>36</sup>

## Future Directions

Research into childhood stroke is at early stages. Almost all management strategies are extrapolated from adult data. The current standard of care hyperacute therapies in adults are not currently approved for use in children. Management protocols and guidelines specific to childhood stroke are just emerging. The challenges faced by childhood stroke include patient population numbers, lack of specific assessment measures and treatment safety and efficacy data. This has led to the development of nationwide stroke initiatives both in North America and Europe. Currently, major international collaborations are underway to investigate the safety and efficacy of adult treatment protocols in children. The International Paediatric Stroke Study (IPSS) is one such effort to gain insights into paediatric stroke. The IPSS is a prospective registry collecting information on paediatric stroke from 149 participating health centers across the world, including two Asian centers (<https://app3.ccb.sickkids.ca/cstrokestudy>). Participation in such studies will further enhance our understanding of paediatric stroke especially in relatively understudied regions of the world such as Asia. However, since Asian countries like Pakistan carry huge population numbers, such efforts should be initially organized and carried out at a national level. This requires support from both government and non-governmental organizations.

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