Little is known about risk factors in pediatric and newborn arterial ischemic stroke (AIS). Risk factors regarding pediatric AIS are evolving and include, in order of prevalence: vasculopathy, infection, cardiac disease, sickle cell disease (SCD), and “other” causes. However, as many as 27% of pediatric and most newborn strokes have no identifiable risk factor.1

### Perinatal AIS

The incidence of perinatal AIS, defined as occurring one month before to one month after delivery, is approximately 4 per 10,000 full-term babies.2 Direct causes for newborn stroke are not well understood. Predisposing maternal factors may include chorioamnionitis, premature rupture of membranes, and first-time pregnancy.3 The birthing process itself may be a risk, and AIS is likely polygenic. In neonates with hypoxic ischemic encephalopathy (HIE), 10% of those with severe HIE may have focal infarcts. Thrombophilias and vasculopathies as determined by MRA are rare.3 Perinatal stroke does not usually recur.

### Pediatric AIS

Pediatric AIS is defined as occurring age 1 month through 18 years with a peak at about age 5 years.3 Risk factors include arteriopathies, infection, cardiac disease, blood disorders, and heritability. There is overlapping pathophysiology of many of these risk factors.

### Arteriopathies

Arteriopathies may be acute, transient, or progressive and can occur in about 50% of children with AIS, but estimates vary between series.1 The most common arteriopathies are focal arteriopathy of childhood (FAC), Moyamoya, and arterial dissection.1 FAC is coined by the International Pediatric Stroke Study Group (IPSS). Previous studies show an association with infectious agents such as varicella.1,3,4,5 Additionally, arteriopathies are associated with sickle cell disease (SCD) and congenital hypoplastic vessel abnormalities.3,4,5 Once a stroke occurs the recurrence rate is approximately 30%,6 but in children with vasculopathy, there is a greater risk of recurrence approaching 50% or more.

Moyamoya disease is a chronic noninflammatory occlusive intracranial vasculopathy with stenosis of the supraclinoid internal carotid artery and secondary development of an extensive collateral network giving an appearance on imaging of a “puff of smoke.” Acquired Moyamoya syndrome may be associated with postinfectious vasculopathy, genetic disorders such as NF-1, and cranial irradiation.4,5

Arterial dissection of the cervical and intracerebral arteries may occur in 20% of patients,1 but is less common than this in our experience.

SCD is also associated with a progressive occlusive arteriopathy, and occasionally Moyamoya syndrome. Vasculopathy increases the risk of further strokes even in patients receiving transfusion therapy.7,8

Vasculopathies may be attributable to congenital syndromes and diseases such as PHACE, NF-1, and Down Syndrome. PHACE syndrome is an acronym for Posterior fossa brain malformations, facial hemangiomas, arterial abnormalities, coartation of the aorta and cardiac defects and eye abnormalities.1

### Infection

Infection may account for nearly one quarter of childhood stroke. In a large population-based study, 23% of strokes were attributable to infection, either meningitis or sepsis.1 Infection may cause cerebral ischemia in several ways, including thrombosis via a systemic inflammatory response or direct invasion of the endothelium.9,5 There is likely a polygenic etiology in meningitis.4 Several viral infections are associated with stroke including varicella, HIV, parvovirus B19, and influenza A.3 A case-control study of children with idiopathic AIS noted a history of varicella infection within the preceding 9 months, in 64% of cases and 9% of controls.10 Another study noted the frequency of a prior varicella infection in children with stroke was three times higher than those of published controls.11 AIS has been reported in two pediatric cases after varicella immunization.2 Lastly, recurrence in varicella maybe as high as 50%, which is likely attributable to vasculopathy, frequently seen after this infection.11

### Cardiac Disease

Cardiac disease has been identified in 10% to 30% of children with stroke.1,3 Additionally, cardiac disorders are the most...
frequently noted risk factor in children who are hospitalized with stroke in the United States from 1979 to 2004. Stroke is also a known complication of cardiac surgery as well as cardiac catheterization. The majority of children with a cardiac cause of their stroke have a previous diagnosis of heart disease, and it is rare for stroke to be the initial presentation of cardiac disease. Although any heart abnormality may confer an increased risk of stroke, complex anatomic abnormalities appear to cause the highest risk.

Hematologic Disease

Hematologic disease risk factors include thrombophilia and sickle cell disease (SCD). Thrombophilias are less common as a cause than initially believed; however, children with multiple thrombophilias, thrombophilia with a cerebral arteriopathy, or heart disease have a higher stroke risk. SCD is the most important hematologic risk factor for pediatric stroke. SCD has a 30% lifetime risk for stroke, and two thirds of these patients will have a recurrence. The strongest predictor for stroke is the presence of a prior stroke. This is similar to non-SCD stroke, but the relative risk is probably twice as high in SCD once stroke occurs (30% in non-SCD without vasculopathy versus 60% in all SCD patients).

SCD is a monogenic autosomal disease that confers a high risk for stroke but with phenotypic heterogeneity. Like pediatric and newborn stroke, SCD stroke is polygenic. From a genetic standpoint, certain single nucleotide polymorphisms (SNPs) and haplotypes confer a higher risk. Subtypes of SCD affect the course, for example the thalassemia trait is protective for cerebrovascular disease. Hypertension and nocturnal hypoxemia are both likely risks. In addition, the occurrence of infection, similar to non-SCD stroke, likely predisposes patients to stroke. Clinically, cardiomyopathy and frequent crises are somewhat predictive. In SCD there are risk factors for both the primary and secondary stroke event that can be to some extent predicted by assessing genetic, clinical, and environmental modifiers. However, as the disease progresses, it may not be as amenable to therapeutic intervention, and the assessment of risk needs to be determined as early as possible.

In SCD, the STOP study developed a biomarker for stroke prediction. Using transcranial doppler (TCD), mean peak velocities of greater than 200/cm/s are predictive of stroke. In the event of a high velocity, patients are initiated on prophylactic transfusion therapy, the primary treatment known to prevent stroke. We have speculated that the hyperemia seen in SCD and reflected in the high velocity seen in TCD is a marker for relative insufficient perfusion and poor autoregulation even in the absence of vasculopathy.

Other Risk Factors

Other risk factors include genetic mutations, although these are not usually present in the typical child with stroke (eg, homocysteinuria). There is likely a major gene locus for autosomal dominant Moyamoya disease on chromosome 17p25.3. The effects of genetics and environment on lipid concentrations and coagulation factor levels in pediatric stroke demonstrate an impact of both genetics and environment.

Table. Common Risk Factors for Pediatric AIS

<table>
<thead>
<tr>
<th>Arteriopathies</th>
<th>Focal arteriopathy of childhood (FAC)</th>
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<tr>
<td></td>
<td>Moyamoya</td>
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<td>Arterial dissection</td>
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<td>Sickle cell disease</td>
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<td>Varicella</td>
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<td>Congenital syndromes and diseases</td>
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<td>Infection</td>
<td>Meningitis</td>
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<td>Sepsis</td>
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<td>Viral Infection (varicella, HIV, parovirus B-19, influenza A)</td>
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<td>Cardiac</td>
<td>Congenital heart disease</td>
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<td>Cardiac catheterization</td>
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<td>Hematological</td>
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<td>Sickle cell disease</td>
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<td>Other</td>
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<td>Single nucleotide polymorphisms</td>
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<td>Hypertension</td>
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Conclusion

There is little known about the risks for newborn stroke. Recurrence is rare, and few genetic studies have been attempted. Maternal factors may play a role in a subset, but more needs to be done, including SNP analysis, stroke classification, better understanding of maternal factors, and placental pathology analysis. Of note, newborn stroke rarely recurs; thus determination of the primary risk factors is most important.

There is little known about the risks for pediatric stroke, but it is likely a polygenic disorder. Genetic factors, thrombophilia, and infections need to be better studied. The recent understanding of vasculopathy as a risk factor for a second stroke is likely of great importance. Finally, SCD is better understood, and primary risk factors better predict the first stroke. Ongoing studies of the genetic modifiers need to be determined, and an aggregate score for stroke risk is on the horizon. However, it is crucial to determine the risk for stroke in SCD as early as possible for the therapeutic intervention to be most efficacious and modify the course of the disease.

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Disclosures

None.
References


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