Epidemiology, causes, and morbidities of stroke in the young

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Purpose of review
The purpose is to describe the latest research on epidemiology, causes, and morbidities of stroke in neonates and children.

Recent findings
The global incidence of childhood stroke is approximately 2 per 100 000 person-years, which is significantly lower compared to neonates (20–40 per 100 000 live births) and adults (80–90 per 100 000 person-years). Placental abnormalities are a risk factor for perinatal stroke, although cause is usually multifactorial. In children, nonatherosclerotic arteriopathies and arteriovenous malformations are major causes of ischemic and hemorrhagic strokes, respectively. The perinatal period confers a high risk of stroke and can lead to long-term disability, including motor delay, cognitive or speech impairment, and epilepsy. Recent studies suggest that at least 50% of survivors of perinatal stroke have abnormal neurodevelopmental scores in long-term follow up. Childhood stroke is associated with significant morbidity, including epilepsy, motor impairments, and behavioral disability. Recent studies have also identified an association between pediatric stroke and behavioral disorders, such as attention deficit hyperactivity disorder and autism.

Summary
Perinatal and childhood strokes are important causes of neurological morbidity. Given the low incidence of childhood stroke, prospective research studies on epidemiology, causes, and outcomes remain limited, highlighting the need for continued multisite collaborations.

Keywords
epidemiology, outcomes, pediatric stroke, perinatal stroke

INTRODUCTION

Stroke is an important cause of acquired brain injury in neonates and children and is among the top ten causes of morbidity and mortality in the young. There has been a significant amount of research in the last twenty years on the epidemiology, causes, and outcomes of pediatric stroke. The latest scientific statement from the American Heart Association/American Stroke Association on stroke in neonates and children was published in 2019 [1]. This review will focus on the emergence in pediatric stroke since the publication of the 2019 scientific statement. Acute management updates are covered in an accompanying article.

DEFINITION AND CLASSIFICATION

In this review, we will discuss perinatal (age ≤ 28 days) and pediatric (age > 28 days to 18 years) stroke. Perinatal stroke can be diagnosed as either acute, diagnosed in newborns at or near birth, or as presumed perinatal, diagnosed as chronic infarcts on imaging and presumed to have occurred in the perinatal period [1]. For neonates, we will focus on ischemic stroke as it represents nearly 80% of all strokes in this age group. For childhood stoke, we will cover both ischemic and hemorrhagic causes, as they are equally prevalent.

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EPIDEMIOLOGY

Perinatal stroke

Neonatal period confers a relatively high risk of stroke, estimated at 20–40 per 100 000 live-births. A large retrospective cohort study from the Cleveland Clinic identified 55 of 80 567 newborns from 2010 to 2021 with a diagnosis of perinatal stroke based on brain MRI, which is higher than previously reported incidence rates. In line with prior literature, the vast majority (86%) of stroke lesions were diagnosed as acute ischemic stroke (AIS), with remaining 14% characterized as venous ischemic stroke [2▪▪]. Seizures were the most common clinical presentation occurring in 36 of 55 neonates. A 2023 systematic review and meta-analysis reported the global incidence of perinatal ischemic stroke at 38.6 per 100 000 live-births (two studies), with AIS incidence of 18.5 per 100 000 live-births (nine studies) and venous ischemic stroke of 5.56 per 100 000 live-births (three studies) [3▪].

Childhood stroke

The incidence of stroke in children beyond the perinatal period is relatively low, approximated at 2 per 100 000 [4], with hemorrhagic stroke accounting for half of all pediatric stroke cases [5▪,6–8]. Two meta-analyses retrospectively examined the global and regional incidence of pediatric stroke. Oleske *et al.* [9▪▪] used a hospital database and previously published studies to assess the incidence of pediatric stroke across different age groups. The incidence peaked in the perinatal period (24.6 per 100 000 live births), reached a nadir in the 5 to 9-year age group, and rose again in the 10 to 18-year age group, consistent with prior studies (Fig. 1). Gao *et al.* [3▪] performed a meta-analysis to determine the global incidence of pediatric ischemic stroke and assess its change over time. They found that global incidence varied from 0.9 to 7.9 per 100 000 person-years, with a pooled incidence of 2.09 per 100 000 person-years. AIS was the main subtype of ischemic stroke, with pediatric annual incidence of 0.69 per 100 000 person-year, compared to 18.5 per 100 000 neonates. The authors reported no statistically significant difference in stroke incidence in studies published up to 2011 (eight studies) versus after 2011 (three studies). This finding contradicts a prior investigation that suggested an increase in the global incidence of pediatric ischemic stroke from 1990 to 2013 [10]. Further research is needed to clarify temporal trends in childhood stroke incidence.

There is growing body of evidence that pediatric patients with large vessel occlusion (LVO) strokes can successfully undergo mechanical thrombectomy [11–14]. A retrospective study from Australia examined 166 pediatric AIS cases from 2010 to 2019 and found that LVO was present in 39 patients (23.5%), similar to the rate in adults [15▪▪]. Two abstracts presented at the International Stroke Conference reported similar rates of LVO in patients with vascular imaging [16,17]. Further research is needed to understand the global incidence and selection criteria for acute neurovascular intervention in pediatric AIS.

ETIOLOGY

Perinatal stroke

The cause of perinatal stroke often remains unknown, but there are several maternal and neonatal risk factors that are associated with stroke in this age group. Chorioamnionitis (by clinical diagnosis or placental histology) is a major risk factor for perinatal stroke [2▪▪,18▪]. It is hypothesized that placental infection and inflammation can cause a pro-thrombotic state leading to clot formation and propagation in the newborn. A retrospective cohort study from the Parkland Hospital found that half of the placentas of neonates with stroke had evidence of acute histologic chorioamnionitis compared to a rate of 28% in the control group [18▪]. The study also identified histologic evidence of chronic inflammation, in
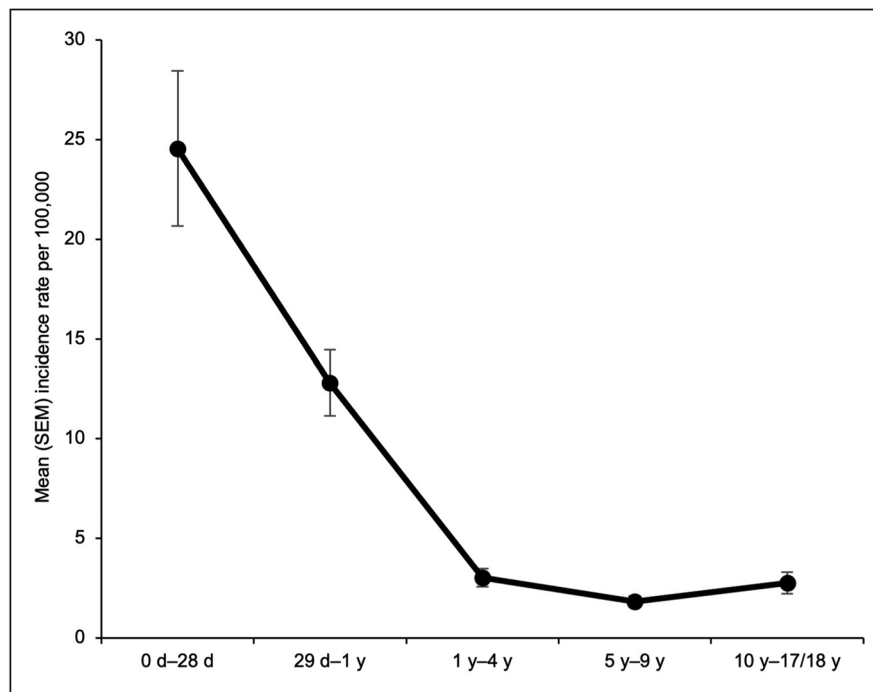
FIGURE 1. Incidence rates of pediatric acute ischemic stroke by age-group per 100 000 children (per 100 000 live births for 0–28 day age-group), 1992–2018. Previously published by Oleske *et al.* [9▪▪].

the form of villitis of unknown etiology, as a risk factor for perinatal stroke. Maternal factors associated with chorioamnionitis are low socioeconomic status, smoking, and inadequate antenatal care [19]. Additional neonatal risk factors include asphyxia, fetal acidosis, congenital heart disease, infection, and prothrombotic gene mutations [20]. It has been hypothesized that most perinatal strokes are multifactorial with genetic factors affecting the threshold for acute stroke in hyperinflamed or hypoxic conditions [21].

Childhood ischemic stroke

The causes of AIS in children and adolescents are diverse and include, but are not limited to, nonatherosclerotic arteriopathies, cardiac causes, and hypercoagulable states (Fig. 2). Arteriopathy is the most common cause of stroke in children, contributing to up to 53% of cases [22]. Unlike atherosclerotic arteriopathy often found in adults, pediatric arteriopathies are often triggered by infection or inflammation [23]. The most common cause of stroke in a previously healthy child is focal cerebral arteriopathy (FCA), a distinct entity that typically presents with basal ganglia infarct and focal narrowing of the distal internal carotid artery (ICA) and its proximal branches following an antecedent illness. The pathophysiology of FCA is thought to be a localized, postinfectious inflammation of the intracranial vessel wall. FCA can progress over days to weeks and progression on neuroimaging correlates with neurologic outcomes at 1 year [24].

Moyamoya arteriopathy is another important cause of stroke in children, contributing up to 10% of all pediatric strokes [25]. Moyamoya is a progressive arteriopathy characterized by stenosis of the intracranial ICA and/or middle and anterior cerebral arteries and the compensatory development of abnormal collaterals in the proximity of stenotic vessels. It can occur as an isolated phenomenon or associated with conditions such as neurofibromatosis, sickle cell disease (SCD), and renovascular disease. Two retrospective studies reported that Moyamoya can present with various clinical phenotypes, including headache, seizures, movement disorder, and stroke [26,27]. Younger age at the time of diagnosis was associated with worse outcome [27].

SCD is the most common hematologic disorder associated with pediatric stroke, increasing the risk 200-fold [1]. Diverse mechanisms underlie stroke in patients with SCD, including large artery occlusion, Moyamoya syndrome, vasculopathy, and small vessel occlusion [28]. Transcranial doppler screening and preventive monthly transfusion can lower the risk of stroke up to 10-fold and is standard of care in the developed countries [29,30]. Lower-cost strategies of reducing risk of stroke in children with SCD, such as hydroxyurea, are an area of ongoing
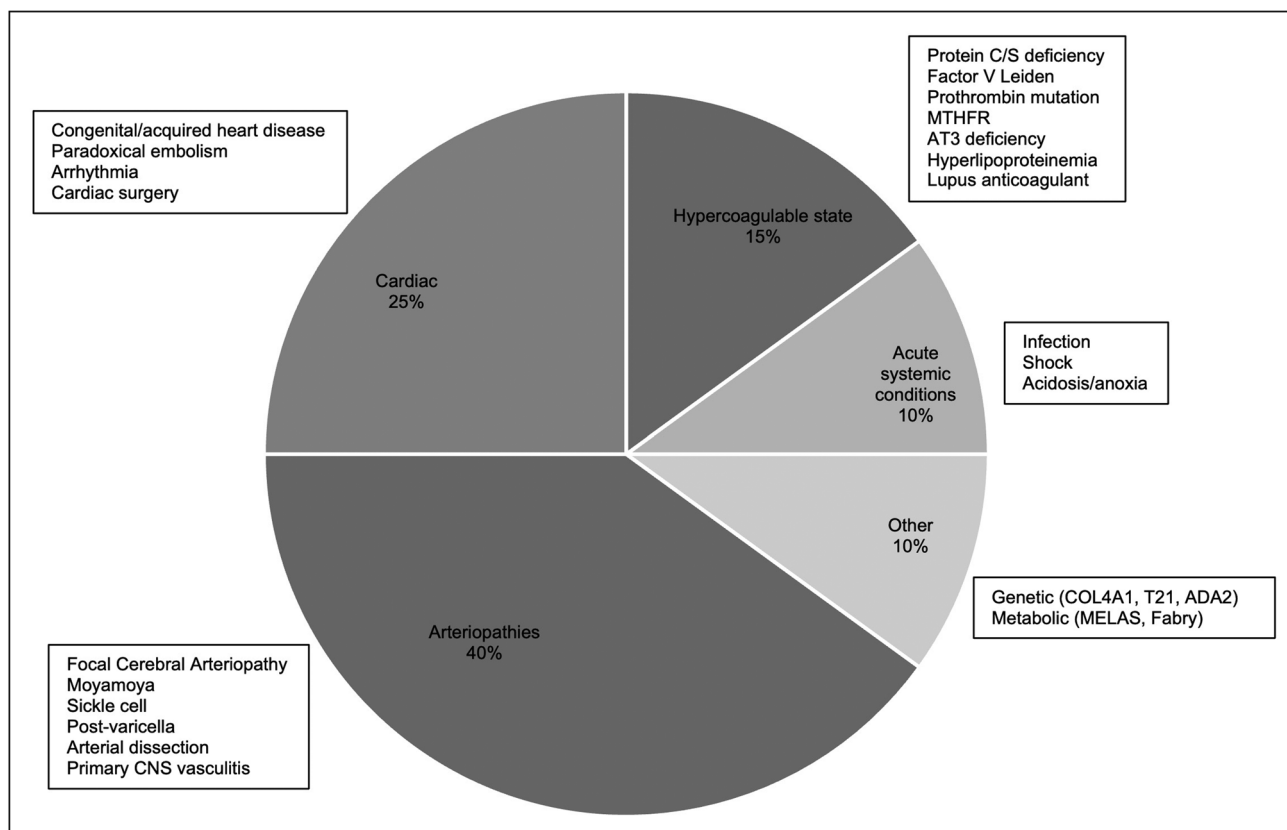
FIGURE 2. Risk factors for childhood acute ischemic stroke [28,48].

research. A feasibility trial of Nigerian children with SCD and abnormal TCD showed that moderate-dose hydroxyurea was well tolerated and effective [31].

Cardioembolic stroke accounts for 25–30% of all childhood strokes and occurs in the setting of congenital heart disease, procedure-related events, or acquired heart disease [32]. A study of 672 children with cardiac causes of AIS found that the majority (74%) of patients had spontaneous AIS while the remaining 26% of strokes occurred peri-procedurally. Patients who had spontaneous stroke were more likely to have a preceding thrombotic event while both groups had similar rates of systemic illness at the time of stroke [33]. Further research is needed to identify early signs and risk factors to aid in prevention of stroke in this population.

Childhood hemorrhagic stroke

Vascular malformations are the most common etiology of nontraumatic hemorrhagic stroke in children, accounting for up to 78% of cases [34]. In patients with vascular lesions, arteriovenous malformations (AVMs) account for most cases (60–70%), while aneurysms (<10%) and cavernous malformations (<20%) are less common in children

[35]. A retrospective cohort study of 243 children admitted with hemorrhagic stroke identified a vascular lesion in 78% of cases, cardiac disease in 7%, and coagulation disorders in 6%, with the latter two being more common in children younger than 2 years [35]. Hemophilia, a congenital deficiency of Factor VIII or Factor IX, is the main coagulation disorder associated with risk for pediatric hemorrhagic stroke. While genetic causes are rare, patients presenting with a ruptured AVM should be screened for a history of frequent nose bleeds or bleeding in the stool, and examined for mucocutaneous telangiectasia, along with a detailed family history to evaluate for possible Hereditary Hemorrhagic Telangiectasia, an autosomal dominant condition associated with mutations in *ACVRL1*, *ENG*, and *SMAD4* genes that increase the risk of AVMs throughout the body [5■].

OUTCOMES

Perinatal stroke

Short-term and long-term morbidities are common in infants who suffer perinatal stroke. A retrospective cohort study from Chile of 33 infants with acute perinatal stroke found that 45% of newborns had a

motor deficit at discharge; larger stroke volume and basal ganglia involvement were independently associated with weakness [36]. Seizures were commonly described short-term morbidity occurring in 27% of infants at the time of hospital discharge. Elgendy *et al.* [2▪▪] reported that many children who suffer perinatal stroke can achieve normal neurodevelopmental scores at 2-year visits, although 16% of them had significant neurodevelopmental delays, five infants (15%) developed hemiplegic cerebral palsy, and one infant (3%) had spastic quadriplegia. Moreover, at 2-year follow up, outpatient physical therapy was required for 24%, speech therapy for 21%, and occupational therapy for 18% of children. While children with large left-sided perinatal strokes can have normal language development secondary to presumed right hemispheric reorganization [37], poststroke epilepsy was identified as an independent risk factor for deficits in both verbal communication and nonverbal intelligence (e.g., problem solving and abstract reasoning) [38,39].

Behavioral conditions are emerging as an important cause of morbidity after perinatal stroke. In a retrospective study from the Hospital for Sick Children, externalizing symptoms of aggression and defiance were reported in as many as 30% of perinatal stroke patients [40]. A Swedish cohort study analyzed 343 children with perinatal stroke and found an almost three-fold increased risk of developing attention deficit hyperactivity disorder (ADHD) [41▪▪]; this risk significantly increased with comorbid epilepsy and/or motor deficits. Another study found that children with perinatal stroke had increased prevalence of autism spectrum disorder (ASD) compared to the general population [42]. ASD was frequently diagnosed late in this population, highlighting the importance of early screening. Finally, the impact of perinatal stroke on parents and family is likely significant though less studied. Recent evidence suggests higher rates of stress, anxiety and depression in parents of children with perinatal stroke compared to normative data [40].

Outcomes in perinatal hemorrhagic stroke are understudied. A single-center retrospective cohort study from Hungary described neurodevelopmental outcomes in 50 term neonates who were found to have a hemorrhagic stroke on MRI [43]. Outcomes were collected at a median age of 60 months; 40% of infants were found to develop according to population norms. The most common morbidities included behavioral problems (24%), epilepsy (22%), and language disorders (18%). Motor disability was documented in eight infants (16%). Parietal lobe hemorrhage was associated with motor and cognitive deficits, while basal ganglia and/or thalamic hemorrhages increased the odds of epilepsy seven-fold.

Further prospective studies are needed to understand the spectrum of neurologic morbidities after perinatal stroke.

Childhood ischemic stroke

Childhood stroke carries a significant risk of neurologic morbidity. Motor disability is common, occurring in 40–90% of patients depending on the follow-up period [44]. Epilepsy is another important cause of morbidity following ischemic stroke. A retrospective study from the Swedish National Registry identified 1220 children who were diagnosed with AIS from 1969 to 2016 and found that 219 (18%) children were diagnosed with epilepsy during follow-up (compared to 0.7% of matched controls) [45]. Survivors of childhood stroke had much lower incidence rate of epilepsy (11.6 per 100 000) compared to perinatal stroke patients (27 per 100 000). The highest risk of developing epilepsy was in the first 6 months poststroke, but the risk remained elevated even 20 years after stroke.

One of the few prospective studies in pediatric AIS examined social cognition at 5 years following stroke in a mixed cohort of 12 children with perinatal stroke and 18 children with childhood stroke [46▪▪]. Relative to 37 healthy controls, children with AIS displayed worse social cognitive abilities across measures of cognitive theory of mind, basic facial emotion processing, and affective theory of mind. Larger infarcts, cortical-subcortical disease, and involvement of multiple arterial territories were associated with worse social cognition scores. Further research is needed to examine whether the magnitude of the effect of AIS on social cognitive abilities differs as a function of developmental stage at the time of stroke.

Evidence suggests survivors of pediatric stroke are at a high risk of behavioral disorders including ADHD and ASD [41▪▪,47]. A Swedish retrospective found that pediatric AIS increased the risk of developing ASD three-fold in survivors of childhood stroke [47]. In addition, stroke survivors had a two-fold increased risk of ADHD [41▪▪]. Comorbid epilepsy and motor disability increased the risk of ASD and ADHD.

Childhood hemorrhagic stroke

Studies investigating outcomes following childhood hemorrhagic stroke are sparse. In a retrospective cohort of 231 children with hemorrhagic stroke, more than half (132, 57%) had favorable outcome at a median of 33 months, with 58 children (44%) having no residual deficits [35]. The authors then performed a meta-analysis of 19 studies and found

that complete recovery occurred in only 27% of patients, with an aggregate case-fatality rate of 17% [35]. Aneurysmal hemorrhage was associated with significantly worse outcome compared to AVM-related hemorrhage, and patients younger than 4 years were more likely to have poor functional outcome or to have died by the last follow-up.

CONCLUSION

Perinatal and childhood strokes are important causes of neurological morbidity. Given the low incidence of childhood stroke, prospective research studies on epidemiology, causes, and outcomes remain limited, highlighting the need for continued multisite collaborations.

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