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Etiology and Risk Factors for Strokes in the Pediatric Population

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Abstract

Pediatric arterial ischemic stroke (AIS) and hemorrhagic stroke represent a relatively uncommon yet significant source of neurological challenges for neonates and children, resulting in outcomes such as hemiparesis, intellectual disabilities, and epilepsy. The etiology of pediatric strokes differs from the typical causes seen in adult stroke cases. Therefore, understanding the specific risk factors associated with strokes in children is crucial for facilitating early diagnosis, which regrettably remains frequently delayed. AIS incidence varies due to factors such as patient age, types of cerebral vascular diseases, other chronic conditions and geographic location. In this comprehensive review, we delve into the epidemiology, clinical manifestation and risk factors linked to arterial ischemic stroke and hemorrhagic stroke in neonates and children.

Key words: pediatric stroke, arterial ischemic stroke, hemorrhagic stroke, child, risk factors, etiology

Introduction

Stroke is traditionally defined as a neurological impairment resulting from the sudden focal damage to the central nervous system (CNS), caused by vascular factors such as cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). This condition, while affecting the CNS, represents a significant global health concern due to its substantial impact on disability and mortality rates across the world. [1] This debilitating condition encompasses various forms, with cerebral infarction stemming from a lack of blood

flow to a specific brain area, intracerebral hemorrhage arising from bleeding within the brain tissue, and subarachnoid hemorrhage resulting from the rupture of blood vessels on the surface of the brain. Collectively, these different stroke types share the common characteristic of causing neurological deficits, which can range from mild to severe, with far-reaching consequences for affected individuals [1,2,3].

The implications of stroke extend beyond individual health, as it represents a major societal and healthcare challenge. The burden of stroke is particularly pronounced due to the often long-lasting and sometimes permanent impairments it can cause, impacting not only the affected individuals but also their families and caregivers. Moreover, stroke places a significant strain on healthcare systems worldwide, as it requires specialized medical interventions, rehabilitation, and ongoing care to support those affected on their path to recovery. Although the occurrence of acute stroke in pediatric patients is considerably less frequent when compared to adults, the percentage of young patients who experience enduring neurological impairments, the consequential effects on their quality of life, and the associated healthcare expenses can be significantly greater in children. [2]

Classification and Epidemiology

The classification of Acute Ischemic Stroke (AIS) based on age divides this clinical syndrome into two distinct categories: perinatal stroke, also occasionally referred to as neonatal stroke, and childhood stroke. Perinatal stroke is characterized by strokes occurring during the perinatal period, starting at around 20 weeks (sometimes 28 weeks) of gestation and extending through the first 28 days following birth. On the other hand, childhood stroke encompasses a broad age range, spanning from 28 days after birth up to 18 years of age [3].

Similar to adult cases, pediatric stroke can also be classified based on whether the underlying cause is hemorrhagic or ischemic. Ischemic strokes encompass arterial ischemic stroke (AIS) and venous infarction, which can result from conditions such as cerebral sinovenous thrombosis (CSVT) or cortical vein thrombosis. In cases of CSVT, the occlusion of venous sinuses may or may not be accompanied by hemorrhage. [3]

Recurrent strokes, in contrast, refer to multiple stroke incidents occurring over time within the same patient. The incidence of recurrent strokes can be as high as 12% within the first year following the initial stroke event, with the greatest risk observed in patients with arteriopathy or cardiac diseases. In some cases, the recurrence risk may even reach up to 27% [5].

The reported incidence of strokes in pediatric patients exhibits a range between 1.3 and 13 cases per 100,000 per year, and in neonates, it can be as high as 25 to 40 cases per 100,000 births [3,4,9,16]. This incidence has displayed an upward trajectory over recent decades, likely attributed to improved stroke detection methods and the wider availability of advanced imaging techniques [7]. The incidence of strokes in childhood is closely linked to age, with the highest occurrence observed during the perinatal period, accounting for up to 25% of reported cases [8]. Subsequently, the incidence decreases with increasing age. Excluding the perinatal period, the highest documented incidence of childhood strokes is seen in children below five years of age [3]. In the perinatal period, arterial ischemic stroke (AIS) with arterial ischemic etiology dominates, accounting for up to 80% of cases [12,13]. However, in childhood strokes (excluding the perinatal period), the etiology is evenly divided between hemorrhagic and ischemic strokes, with a slight predominance of AIS, which constitutes approximately 58.6% of cases, compared to 38.6% [10]. This multifaceted landscape of pediatric stroke incidence underscores the importance of ongoing research and effective early detection to address this evolving public health concern.

Etiopathogenesis and Risk Factors

The development of pediatric arterial ischemic stroke (AIS) appears to differ from that in adults, where well-known risk factors include atherosclerosis, diabetes, hypertension, smoking, metabolic syndrome, insulin resistance, and chronic inflammatory conditions [3]. In the case of AIS in children, the range of risk factors is even more extensive. However, within specific age groups, certain factors seem to carry more significance than others [16] (table 2).

Arterial Ischemic Stroke in Neonates

Risk factors for perinatal arterial ischemic stroke encompass a combination of maternal and neonatal factors. This includes the proper activation of coagulation factors in the mother and lower levels of these factors in the infant in the period just before and after birth.[3] Reported and presumed risk factors associated with perinatal stroke include infertility, primiparity, gestational hypertension, oligohydramnios, pre-eclampsia, chorioamnionitis, maternal fever, premature rupture of membranes, prolonged or instrumental/surgical delivery, birth asphyxia, trauma, early sepsis, cardiac disease, dehydration, hypercoagulable states (including Factor V Leiden, Prothrombin G20210A mutation, Methylenetetrahydrofolate reductase mutation—MTHFR, Protein C or S deficiency, increased levels of factor VIII, IX, XI, fibrinogen, lipoprotein (a), hyperhomocysteinemia, and antiphospholipid syndrome), as well as vasculopathies, primarily arteriopathies.[3,4,5,6,13] However, in many cases, the cause may remain unrecognized. [13]

Neonatal cerebral sinovenous thrombosis (CSVT) is often linked to various conditions, including complications during gestation or delivery, dehydration, sepsis, meningitis, cardiac defects, and coagulation disorders. While these factors are commonly regarded as potential risk factors, it's important to note that there is a lack of controlled studies that definitively confirm these associations. [3]

Hemorrhagic Stroke in Neonates

Neonatal brain hemorrhage can be caused by various factors, including coagulopathy, thrombocytopenia, trauma, and, less commonly, structural vascular lesions. Many neonates with hemorrhagic stroke have no specific identifiable cause, but some risk factors include postmaturity, emergency cesarean delivery, fetal distress [3]. Mutations in COL4A1 should be considered in neonates with cerebral hemorrhage, porencephaly, glaucoma, or cataracts [25]. Intracranial hemorrhage in newborns can be associated with either acquired or congenital coagulopathy. Hemorrhagic disease of the newborn is a concern in regions where routine vitamin K supplementation is not administered to neonates. In the United States, cases of intracranial hemorrhage have been reported in babies whose caregivers declined vitamin K administration after birth [26]. Intracranial hemorrhage has also been documented in neonates with hemophilia A and other hereditary coagulopathies [3,24].

Arterial Ischemic Stroke in Children

Identified risk factors for childhood arterial ischemic stroke (AIS) encompass a range of conditions (table 1), including arteriopathies, chronic systemic diseases associated with inflammation, sickle cell anemia, cardiac diseases, hypercoagulable states (thrombophilia), metabolic disorders, trauma, infection, dehydration, and cancer [4]. There is a higher reported incidence of AIS among individuals of Black race and male gender [3,15,22]. It's not unusual for a single patient to have several of these contributing factors. When multiple factors coincide in a patient, the risk of recurrent ischemic events becomes more pronounced [15].

Depending on the publication, cardiac causes and arteriopathies are mentioned as the most common. [4,15]. Cardiac causes include congenital heart disease, valvular diseases, endocarditis and myocarditis. Particularly high risk is observed in children with congenital heart disease, where the AIS risk is 19-fold higher [3,4]. Arteriopathies, affecting both intra- and extracranial arteries, such as Moyamoya, craniocervical arterial dissection (CCAD), vasculitis, focal cerebral arteriopathy (FCA) and post-varicella arteriopathy are found to be risk factors in up to 29% of reported cases [19]. Moyamoya disease is defined by an ongoing narrowing of the blood vessels in the brain, leading to recurring episodes of cerebral ischemia. In children with moyamoya, transient ischemic attacks are frequently linked to hyperventilation, indicating that reduced blood flow, rather than thrombotic vessel blockage, plays a prominent role as the mechanism in these cases. [23]. Focal cerebral arteriopathy (FCA) is believed to be associated with a post-infectious inflammatory process. It typically affects school-aged children to adolescents with no specific gender or racial preference. This arteriopathy is characterized by its acute, monophasic, and unilateral nature, involving irregularities or stenosis of the distal internal carotid artery and its proximal branches. The suggested mechanism is an inflammatory response triggered by viruses. [14] Another arteriopathy caused by infections is post-varicella arteriopathy as a consequence of chickenpox [15]. Vascular wall dissection, primarily linked to neck trauma, is a noteworthy concern. Imaging of the blood vessels from the head and neck down to the aortic arch is an integral part of the recommended neuroimaging methodology for children suspected of having a stroke. [15] An additional set of factors that play a role in the development of pediatric arterial ischemic stroke involves coagulation abnormalities, whether they are congenital or acquired, recognized as either thrombophilia or a prothrombotic condition. Thrombophilia is identified in 20–50% of children with AIS, a notably higher rate compared

to adult AIS patients [6]. Sickle cell disease (SCD) represents a significant regional AIS risk factor, particularly prevalent in regions with a higher incidence of SCD, such as Sub-Saharan Africa, South Asia, the Middle East, and the Mediterranean. The peak incidence of SCD-related AIS occurs in children between 2 and 5 years of age [21]. In children with cancer, stroke occurs in about 1% of cases, with an equal occurrence of both acute arterial ischemic and hemorrhagic strokes. Notably, children with leukemia and brain tumors have been identified as having the highest susceptibility to stroke. [20]

In a considerable percentage of AIS cases (50–80%), at least one risk factor has been identified, while in 25% of cases, no specific risk factor can be pinpointed, categorizing the AIS as idiopathic [17].

Early diagnosis and treatment of cerebral sinovenous thrombosis (CSVT) require both a high level of suspicion and an understanding of the risk factors involved. CSVT often occurs due to the convergence of multiple age-related factors that promote blood clot formation, many of which are subject to modification. [3,27] These factors encompass conditions like fever, anemia (particularly iron deficiency), dehydration, and infection, frequently localized in the head and neck, such as otitis media, mastoiditis, sinusitis, orbital cellulitis, and meningoencephalitis. In addition to these, chronic systemic and inflammatory conditions, including inflammatory bowel disease, Behçet syndrome, systemic lupus erythematosus (linked to lupus anticoagulant and antiphospholipid antibodies), homocystinuria, protein-losing disorders like enteropathy and nephropathy, and liver failure leading to hypercoagulability, are associated with CSVT. Congenital heart disease, childhood malignancies such as acute lymphoblastic leukemia and central nervous system tumors, and the use of prothrombotic medications like steroids and estrogen-containing contraceptives can also contribute to CSVT [27,28].

Table 1. Risk factors for arterial ischemic stroke in pediatric population [11,14,15,16,17]

Cardiac	Congenital heart disease; Valvular heart disease; Endocarditis; Myocarditis.
Arteriopathies	Moyamoya disease; FCA - focal cerebral arteriopathy of childhood; Craniocervical arterial dissection (CCAD); Post-varicella arteriopathy; Vasculitis secondary to bacterial meningitis; Congenital blood wall defects e.g. fibromuscular dysplasia, hypoplasia.
Hypercoagulable state, thrombophilia	<p>Congenital:</p> <p>High lipoprotein(a)(lp(a) serum concentration;</p> <p>Protein C (PC) deficiency;</p> <p>Protein S (PS) deficiency;</p> <p>Antithrombin III (ATIII) deficiency;</p> <p>Activated protein C resistance (APCR);</p> <p>Genetic polymorphisms of genes of coagulation factors:</p> <p>Factor V G1691A;</p> <p>Factor II G20210A;</p> <p>MTHFR C667T;</p> <p>Factor XIII Val34Leu;</p> <p>Fibrinogen A (FGA) Thr312Ala;</p> <p>Fibrinogen B (FGB) G455A;</p> <p>Acquired:</p> <p>Antiphospholipid syndrome APS.</p>
Infections	Upper respiratory infections; Bacterial meningitis;

Hematological/oncological	Sickle cell anemia; Cancers
Genetic/metabolic	Trisomy 21; Neurofibromatosis type 1; Vascular Ehlers - Danlos; Connective tissue disorders.
Others	Intoxications (e.g. cocaine, amphetamines); Neck traumas causing vascular wall dissection.

Table 2. Age-Specific Prevalent Risk Factors in AIS in children (according to Jeong et al. [16])

Age	Age-specific prevalent risk factors
1-12 months	Central nervous system infections Cardiac diseases Severe dehydration
1-5 years	Moyamoya disease Cardiac diseases Inflammatory vasculopathy
6-11 years	Moyamoya disease Metabolic diseases Hypercoagulable states
More than 12 years	Cardiac diseases Metabolic diseases Hypercoagulable states

Hemorrhagic Stroke in Childhood

Non-traumatic, spontaneous intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), and subarachnoid hemorrhage (SAH) occurring in childhood are typically associated with structural lesions in approximately 75% of cases. Among these structural lesions, brain arteriovenous malformations are the most frequently identified culprits, with around 10% of hemorrhages having no identifiable cause and remaining idiopathic. [3,29,30]. Structural

causes of hemorrhagic strokes in children include: aneurysms, spontaneous hemorrhages into tumors and arteriovenous malformations. The most common hematologic causes are Hemophilia A or B and von Willebrand disease. Rare causes include factor VII, II or XIII deficiency and Vitamin K-dependent clotting factor deficiency. [3]

Clinical Presentation

Early diagnosis of arterial ischemic stroke through immediate imaging is essential for initial management. However, diagnosing strokes in children can be challenging due to age-related differences in symptoms. Children, especially newborns, infants, toddlers, and small children, may exhibit non-specific or atypical stroke symptoms, leading to a longer median diagnosis time compared to adults. The interval from initial symptoms to hospital admission varies widely, with a median diagnosis delay of 15 to 24 hours [3].

Perinatal stroke

Perinatal strokes can manifest through various clinical presentations, including seizures, apnea, focal weakness, and hemiparesis. In cases of perinatal stroke, new-onset seizures, typically characterized by focal motoric unilateral seizures, are the most common symptoms, occurring in up to 94% of newborns (compared to 17-34% in childhood stroke) [3]. Notably, some neonates with neonatal stroke didn't exhibit seizures, particularly those with hypoxic-ischemic encephalopathy (HIE) as the underlying cause [13]. Newborns also frequently display non-specific cardiorespiratory syndromes [4].

Pediatric stroke

Pediatric arterial ischemic stroke typically manifests as a localized neurological impairment. The most frequent deficit is hemiparesis, which can sometimes be mistaken for conditions like seizures or Todd's paralysis, meningitis/encephalitis, migraine, or demyelination, all of which can mimic stroke symptoms. [16] Other common focal neurological deficits include dizziness, difficulty speaking, double vision, and lack of coordination. Seizures are a common occurrence at the onset of stroke in both ischemic and hemorrhagic cases, more so in children compared to adults. They can affect up to 50% of children and are not limited to

any specific age group. [18]

Table 3. Age-Dependent Stroke Symptoms in Children

Neonates	Older children (28 day - 18 years)
Seizures Apnoe, cardiorespiratory symptoms Focal weakness Hemiparesis Altered consciousness Feeding intolerance	Hemiparesis Dizziness Speech disorder Double vision Lack of coordination Facial unilateral weakness Altered consciousness

Summary

Pediatric strokes differ from adult strokes in their etiology and risk factors. Risk factors for perinatal arterial ischemic stroke include a combination of maternal and neonatal factors, such as coagulation factors, gestational conditions, birth-related complications, and hypercoagulable states. Hemorrhagic stroke in neonates can be due to coagulopathy, thrombocytopenia, trauma, and structural vascular lesions, with some cases having no identifiable cause. Childhood AIS risk factors encompass arteriopathies, chronic systemic diseases, sickle cell anemia, cardiac conditions, hypercoagulable states, metabolic disorders, trauma, infection, dehydration, and cancer. Multiple risk factors can coincide in a single patient, increasing the risk of recurrent ischemic events. Cardiac causes and arteriopathies, including Moyamoya disease and focal cerebral arteriopathy, contribute significantly to childhood AIS. Coagulation abnormalities, known as thrombophilia or prothrombotic conditions, are identified in a substantial percentage of children with AIS. Hemorrhagic strokes in childhood are often associated with structural lesions, with brain arteriovenous malformations being the most common cause. Hematologic causes of hemorrhagic strokes in children include hemophilia, von Willebrand disease, and rare coagulation factor deficiencies.

Neonatal strokes can manifest with various clinical presentations, including seizures, apnea, focal weakness, and hemiparesis. Pediatric arterial ischemic stroke typically presents with

localized neurological deficits, with hemiparesis being the most common. Other focal neurological deficits include dizziness, difficulty speaking, double vision, seizures and coordination problems.

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