Review Article

Pediatric Arterial Ischemic Stroke: Current Insights and Challenges

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ABSTRACT

Paediatric arterial ischemic stroke (AIS) is a significant cause of acquired brain injury in children, leading to considerable morbidity and mortality. The incidence of AIS in children ranges from 1.2 to 8 cases per 100,000, with diverse etiologies that differ from adults, including congenital abnormalities and lifestyle factors. Recent studies highlight the exacerbating role of infections, such as influenza, and the importance of vaccination in prevention. Diagnosis remains challenging due to nonspecific symptoms and the need for rapid imaging techniques, with vascular imaging being crucial for accurate etiological diagnosis. The management of pediatric AIS requires tailored strategies, including the use of thrombolysis and mechanical thrombectomy, although evidence for these treatments in children is limited. Recovery outcomes are influenced by early intervention, access to rehabilitation services, and parental involvement. The establishment of dedicated pediatric stroke centres and standardized protocols are essential for improving diagnosis and treatment outcomes. Additionally, ongoing research is necessary to develop evidence-based guidelines specifically for pediatric stroke management, addressing the unique needs of this vulnerable population to enhance recovery prospects and quality of life for affected children.

Key words: infantile stroke, pediatric age group, stroke, etiology, diagnosis, risk factors, management, childhood

Infantile stroke, also known as pediatric stroke, refers to a stroke that occurs in infants and children, typically under the age of 18. While strokes are often associated with older adults, they can also affect the very young, leading to significant morbidity and long-term developmental challenges. Infantile strokes can manifest as either ischemic strokes, where blood flow to the brain is obstructed, or hemorrhagic strokes, where there is bleeding in the brain. The causes of stroke in infants can vary widely and may include congenital heart defects, blood clotting disorders, infections, or trauma. Symptoms can be subtle and may include sudden changes in behavior, weakness on one side of the body, seizures, or difficulty with coordination and movement [1].

Early recognition and intervention are crucial in managing infantile strokes. Prompt diagnosis often involves neuroimaging techniques such as MRI or CT scans, which help determine the type and extent of the stroke. Treatment options may include anticoagulants, rehabilitation therapies, and addressing underlying risk factors [2]. As awareness of infantile strokes grows, it becomes increasingly important for healthcare providers, parents, and caregivers to understand the signs and symptoms to ensure timely medical attention. Ongoing research aims to improve outcomes for affected children, focusing on both immediate treatment and long-term support strategies [3].

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METHODS

This Mini review aimed to discuss various aspects of pediatric stroke, from the published data between 2014 to 2024, retrieved from databases like PubMed and Google Scholar. Peer reviewed original articles, systematic reviews, meta-analyses, and case reports published in English were included in this review. The following keywords and combination of the words like "infantile stroke," "pediatric age group," "stroke," "etiology," "diagnosis," "risk factors," and "management," "childhood," and "causes" were used to search and retrieved the articles. The articles published in other than English language, those not peer-reviewed, conference papers, editorials and stoke in adult excluded from this review.

The finding from the selected studies aimed to enhance understanding of pediatric stroke and its underlying causes,

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thereby contributing to the development of improved management strategies.

RESULTS

A total of 100 articles were reviewed, out of which 38 articles were shortlisted. Only these 38 articles were included, as other articles were published in languages other than English, not peer-reviewed, conference papers, editorials or stoke in adult excluded from this review (Figure 1).

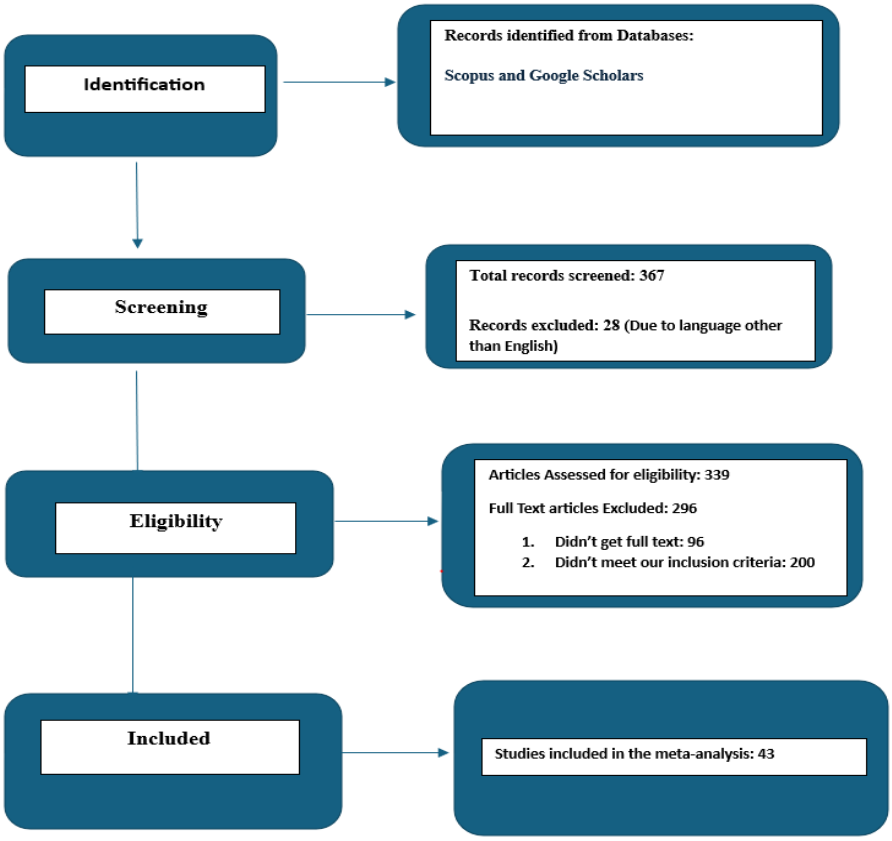

Figure 1

DISCUSSION

1. Overview

The incidence of pediatric stroke is less common than adult stroke, but its potential for considerable death and long-term morbidity makes it a serious health concern. Inadequate clinical awareness and limited management approaches are necessary in view of the difficulties in making an early diagnosis, which are often complicated by the variety and nonspecificity of symptom presentation [1]. The reported incidence of childhood stroke varies widely, ranging from 2.5 to 13 per 100,000 children per year. The mortality rate for strokes in children is estimated to be between 10% and 25%, with haemorrhagic stroke showing a significantly higher mortality rate than ischemic stroke [4]. Hemorrhagic stroke is about twice as common in developing countries, while ischemic stroke is historically 4 to 5 times more prevalent in developing countries compared to developed ones. After an initial stroke, up to 25% of children may experience a recurrent stroke [4].

Although the structural anatomy of the pediatric brain closely resembles that of adults, there are numerous physiological differences that lead to varied stroke presentations. Pediatric cerebral hemodynamic do not match those of adults until around age eight. Before this age, children's brains are more metabolically active, using up to 200% more glucose than an adult brain at age five. This increased demand for cerebral blood flow makes them more vulnerable to focal neurological damage during hypoglycaemic episodes [4]. According to DeVeber et al., seizures are the most common initial symptom of stroke in neonates, while older children more frequently present with focal deficits, particularly hemiparesis. Seizures are also common across all ages, occurring in 37% of participants in relevant studies [38]. A study conducted by Cole et.al identified 86 cases of neonatal hemorrhagic stroke (NHS), with 51 infants confirmed to have NHS, revealing a predominance of idiopathic cases (67%) and hemorrhagic transformation of primary ischemic injuries (35%). The incidence of pure NHS was found to be 1 in 9,500 live births, with most cases presenting in the first week of life, often with seizures and encephalopathy. While acute neurosurgical interventions were rare, the temporal lobe was the most common site of NHS [4].

Significant variations in the sensitivity and positive

predictive value (PPV) of pediatric stroke diagnoses in administrative healthcare data are highlighted by Bindslev et al.'s systematic review. The percentage points for each of the following stroke subtypes had a wide range: spontaneous intracerebral hemorrhage (ICH) (0.62–0.66), cerebral venous thrombosis (CVT) (0.45–0.72), acute ischaemic stroke (AIS) (0.27–0.89), and spontaneous subarachnoid hemorrhage (SAH) (0.52–0.83). This diversity highlights the possibility of errors that arises when these data sources are used for study without first being validated. The review also finds that the use of administrative data is made more difficult by the absence of standardised ICD codes for diagnosing paediatric stroke. According to one study, the sensitivity of ICD-9 codes for AIS was relatively low (33%); although by integrating codes for cerebral palsy, this could be raised to 59% [5]. Despite this improvement, the general correctness of this codes remains a concern.t. Therefore, non-validated administrative data should be used with caution in paediatric stroke research because it may contain significant false-positive and false-negative cases.

The validation of pediatric stroke diagnoses in administrative data is seriously lacking in expertise and that the data, that are now available are only from high-income nations. Therefore, to increase accuracy and dependability in pediatric stroke research, it is imperative to confirm this administrative data through examinations of medical charts and may be add to them with searches for radiological reports [5].

2. Etiology

Several risk factors are associated with pediatric stroke, including hypertension, dyslipidemia, and tobacco exposure. The high prevalence of ICD codes related to tobacco exposure in pediatric ischemic stroke was particularly notable, suggesting a potential area for further investigation and intervention. The role of non-classic pediatric stroke risk factors, such as hypertension and dyslipidemia, raises important questions about their contribution to stroke pathogenesis in children and highlights the need for additional research [6-8].

Investigating these factors are crucial, as the unique aspects of pediatric strokes differ from those in adults, and a clearer understanding could lead to improved diagnostic and therapeutic strategies. Addressing these gaps in knowledge will not only enhance our comprehension of pediatric acute ischemic stroke (AIS) but also inform better clinical practices and ultimately improve outcomes for affected children. Arteriopathies, cardiac disorders, infections, and other risk factors play crucial roles in the development and recurrence of pediatric stroke. Arteriopathies, including focal cerebral arteriopathies and moyamoya disease, contribute significantly to stroke risk, while cardiac conditions like congenital heart defects often lead to cardioembolic strokes [9].

Approximately half of pediatric ischemic strokes occur in children without any identifiable predisposing condition, known as cryptogenic stroke. Around 80% of children with ischemic stroke have cerebrovascular disease, and hypercoagulable states linked to various prothrombotic risk factors are also implicated [1].

Although many stroke symptoms are nonspecific and can be attributed to other causes, in about 25% of pediatric stroke cases, multiple risk factors can be identified, indicating the need for thorough investigation even if only one risk factor is initially apparent. Cardiac disease is the leading cause of pediatric stroke, accounting for up to one-third of all acute ischemic strokes. Embolic clots in children with conditions such as cardiomyopathy, rheumatic heart disease, prosthetic valves, or valvular infections can lead to stroke [1].

Sickle cell disease and prothrombotic disorders are common causes of pediatric stroke, contributing to both arterial and venous events. Infections like varicella, HIV-related vasculitis, mycoplasma, and chlamydia infections, as well as bacterial meningitis, tuberculosis meningitis, and viral encephalitis, are known risk factors due to their potential to cause local vasculitis and thrombosis. Arteriovenous malformations (AVMs) are a leading cause of hemorrhagic stroke in children after infancy and can also contribute to thrombotic strokes. Moyamoya disease, characterized by progressive stenosis or occlusion of the intracranial internal carotid arteries, is associated with approximately 6% of childhood strokes. Additionally, conditions such as marfan syndrome, tuberous sclerosis, homocysteinuria, and deficiencies in folic acid or vitamin B12 are linked to a higher incidence of acute ischemic stroke. Drug abuse, including substances like amphetamines, ecstasy, cocaine, phencyclidine, and glue sniffing, has also been associated with cerebral infarctions and hemorrhages in some pediatric patients [1].

In children with sickle cell disease (SCD), the abnormal sickle-shaped red blood cells can obstruct blood vessels, leading to reduced blood flow and subsequent ischemic damage in the brain. This interplay between substance abuse and underlying medical conditions underscores the complexity of stroke risk in children, necessitating comprehensive assessments and interventions to mitigate these dangers. Chronic anemia, endothelial dysfunction, and inflammation further increase the risk of stroke in these children. Without early intervention, such as regular blood transfusions or hydroxyurea therapy, children with SCD are at particularly high risk for recurrent strokes. Early diagnosis and targeted management of these risk factors are crucial for stroke prevention and improved outcomes. In the case of SCD, routine screening, transfusion therapy, and stroke prevention strategies have been shown to reduce the incidence of AIS significantly [10].

Furthermore, chorioamnionitis has been strongly linked to placental disease, with recent studies indicating that its presence increases the odds of perinatal arterial ischemic stroke (PAIS) by a factor of 3.63 (95% CI, 1.31-10.03). This

highlights the importance of addressing both hematological and perinatal factors in the comprehensive management of stroke risk in children. Exposure to recreational drugs during pregnancy is also significantly associated with a higher risk of PAIS (OR, 5.66; 95% CI, 2.45-13.09), whereas tobacco exposure does not show a similar association (OR, 1.23; 95% CI, 1.00-2.57). Tobacco is believed to affect the placenta by chronically reducing blood flow and creating a hypoxic environment, while vasoactive drugs like cocaine or methamphetamine may more directly trigger thromboembolic events in the placenta, leading to focal arterial ischemic injury in the fetal or neonatal brain [11].

In a case series conducted by Jenny Lin, two patients had moyamoya syndrome, while the third patient had focal cerebral arteriopathy. All three patients had underlying arteriopathies that were made worse by concurrent influenza infections. This implies that whereas arteriopathies are important risk factors for pediatric AIS, simple illnesses such as influenza might serve as important initiators of stroke in children already predisposed to the condition. The results emphasize the significance of taking recent infections and pre-existing vascular disorders into account when evaluating pediatric stroke cases [12].

Recent studies have demonstrated a strong association between minor childhood infections and arterial ischemic stroke (AIS), with the highest risk occurring in the 3 days following an infection. Acute herpesvirus infections, particularly primary infections, appear to be a major risk factor for childhood AIS, and certain pathogen combinations like herpesviruses and parvovirus B19 may further increase stroke risk. Understanding the specific pathogens and inflammatory processes underlying different childhood stroke subtypes is crucial for developing targeted preventive and therapeutic strategies [9].

Herpesviruses, particularly herpes simplex virus 1 and 2, may trigger acute ischemic stroke (AIS) in children, even when the infection is asymptomatic. The Vascular effects of Infection in Pediatric Stroke (VIPS) study found serological evidence of acute herpesvirus infection in 45% of pediatric AIS cases, with HSV-1 being the most common [13]. However, most of these infections were sub-clinical and would have been missed by relying solely on clinical history or a single acute blood sample. The VIPS study demonstrated that acute herpesvirus infection doubles the odds of childhood AIS, even after adjusting for age, race, and socioeconomic status. This suggests that herpesviruses may act as a trigger for stroke through an inflammatory mechanism, regardless of whether the infection causes overt symptoms. While these findings raise the possibility that antiviral medications like acyclovir could play a role in secondary stroke prevention, further research is needed to confirm a causal relationship between herpesvirus infection and childhood AIS. Prospective studies with comprehensive serological testing and longitudinal follow-up would help clarify the link between viral infections and stroke risk in children. In the meantime, clinicians should be aware that the absence of clinical signs of infection does not rule out an acute herpesvirus infection as a potential contributor to AIS in children [13].

A case study conducted by Christopher Troy showed a case of a child experiencing acute ischemic stroke due to osteosarcoma embolism, highlighting the increased stroke risk in pediatric cancer patients, attributed to hypercoagulability and potential tumor metastasis. The embolism likely originated from a pulmonary nodule, emphasizing the need for careful monitoring of cancer patients for neurological complications. Understanding the mechanisms behind such rare occurrences can aid in developing targeted interventions and improving outcomes for affected children [14].

Hemorrhagic Stroke (HS) is more common in younger infants, with non-localizing or diffuse clinical presentations in children under two years of age. The leading causes of HS were coagulation disorders in 52% of cases, CNS infections in 25%, arteriovenous malformations (AVMs) in 13%, and hematological disorders in 6%. Vitamin K deficiency bleeding (VKDB) emerged as the most significant risk factor for HS in infants, followed by hemophilia. In contrast, vascular malformations, CNS infections, and hematological disorders were more prevalent in children older than two years. Acute pyogenic meningitis, tubercular meningitis, and late-onset neonatal sepsis with meningitis were associated with HS [15].

Factors associated with idiopathic Neonatal Hemorrhagic Stroke (NHS) included lower maternal age, primiparity, prior spontaneous abortion, difficult fetal transition, and being small for gestational age. Follow-up revealed poor neurological outcomes in 44% of the cases [4]. These findings underscore the complexity of pediatric stroke, highlighting the need for further research to establish effective treatment protocols and preventive measures, particularly given the significant long-term impact on neurological health and quality of life for affected children and their families. The cause of idiopathic NHS remains largely speculative, with one theory suggesting that a small weakness in an artery may rupture due to the significant blood pressure surge that occurs during the transition to life outside the womb. This hypothesis aligns with existing evidence, including the absence of consistent associations with known risk factors, the presence of larger arteriovenous malformations [4].

2.1 Gender Specificity

During childhood and early adulthood, males show a higher incidence of ischemic stroke compared to females, often accompanied by poorer functional outcomes. This highlights the need for tailored approaches in understanding and managing stroke risk, considering both the biological and structural factors that may contribute to these disparities. This trend emphasizes the importance of recognizing sex differences in pediatric stroke epidemiology, as these differences can

impact treatment approaches and outcomes. While the overall mortality risk for ischemic stroke is significant, the relationship between sex and stroke-related mortality in children remains unclear, indicating a need for further research to explore these interactions [15, 16].

Additionally, females often experience poorer recovery and quality of life post-stroke, highlighting the necessity for sex-specific considerations in clinical trials and treatment protocols for pediatric stroke. Age and sex significantly influence the risk factors associated with ischemic stroke, revealing distinct patterns in pediatric populations. Although the incidence of ischemic stroke is generally lower in children than in adults, males tend to have higher incidence rates and poorer functional outcomes than females during childhood and early adulthood [15, 16]. Unique risk factors for females, such as the use of oral contraceptives and pregnancy-related conditions like preeclampsia, can also affect stroke risk in younger populations. Notably, children exposed to preeclampsia in utero may face long-term health consequences, including an increased risk of stroke later in life, underscoring the importance of maternal health during pregnancy.

The pathophysiology of ischemic stroke in children reveals significant age and sex differences. In vitro studies indicate that male-derived neurons, endothelial cells, and astrocytes are more vulnerable to ischemic damage than their female counterparts. Additionally, females display protective mechanisms against cerebral ischemia that are lost after ovariectomy, suggesting a critical role for estrogens [15, 16]. However, the protective effects of estrogens may diminish with age and hormonal changes, indicating that both hormonal and chromosomal factors contribute to stroke susceptibility and recovery. Research into sex differences in endothelial and glial responses to ischemia further highlights important considerations for pediatric stroke.

Male-derived endothelial cells exhibit greater sensitivity to oxygen-glucose deprivation (OGD), while female astrocytes show resistance to ischemic damage, attributed to estrogen. Moreover, microglial activation patterns differ by sex, with males exhibiting higher activation levels post-ischemia. Understanding these sex-dependent responses is essential for developing targeted therapeutic strategies that consider the unique biological responses of male and female pediatric patients to ischemic injury [15, 16]. Current classifications like the TOAST criteria, primarily developed for older adults, often fail to rapidly identify etiologies in young adults, leading to a high proportion of strokes classified as undetermined. This limitation hinders effective treatment and prevention strategies. Consequently, there is a growing need for new classification systems tailored to young adults [15, 16].

2.2 Regional variations

The etiologies and risk factors for childhood stroke differ significantly from those in adults, with adult cases often linked to arrhythmias and atherosclerosis, which are rarely involved in paediatric strokes. Studies, including the International Paediatric Stroke Study (IPSS), indicate that 50-80% of children with acute ischemic stroke (AIS) have identifiable risk factors, with multiple factors present in about 25% of cases. Risk factor variability is influenced by geography, ethnicity, age, and medical resources. In neonatal stroke, dehydration, infection, and congenital heart disease are more prevalent, while arteriopathies and congenital heart disease are common in older children, particularly in developed countries.

Infectious aetiologies are frequently reported in regions like Saudi Arabia and Northern India, while hemoglobinopathies, such as sickle cell disease, are prevalent in populations with African or Mediterranean heritage. In East Asia, Moyamoya disease is a leading cause. Additionally, inherited metabolic disorders can lead to stroke-like symptoms. There are no established guidelines for assessing these risk factors, but a combination of nonspecific blood tests and specific tests for coagulopathies and other conditions is recommended for evaluation [43].

2.3 Impact of COVID-19

Emerging evidence suggests that SARS-CoV, particularly in the context of COVID-19, may increase the risk of stroke in children, although strokes are still relatively rare in this population. The inflammatory response triggered by the virus, including cytokine storms and vascular inflammation, appears to be a major contributing factor to this elevated risk. COVID-19-associated coagulopathy can lead to blood clot formation, potentially causing ischemic strokes in children. In addition to direct effects on the vascular system, the virus may also exacerbate pre-existing conditions or undetected health issues (such as congenital heart disease, autoimmune disorders, or metabolic issues), further increasing the risk of stroke in children. Children with multisystem inflammatory syndrome (MIS-C), a rare but severe complication of COVID-19, appear particularly vulnerable to stroke due to severe inflammation affecting multiple organs, including the brain and blood vessels. Given the potential for increased stroke risk, heightened clinical vigilance and prompt treatment for children presenting with neurological symptoms during or after a SARS-CoV infection are essential [20].

Ischemic strokes in young adults have diverse and relatively rare causes, such as arterial dissections, autoimmune diseases, and illicit drug use, necessitating specific investigation strategies. Additionally, risk factors vary by age and sex, with pregnancy and contraceptive use being significant for young women, and vascular risk factors becoming more prevalent in those over 35 years [17].

3. Clinical Features

Infantile strokes can present with a range of clinical features (table 1).

Table 1: Clinical features of infantile stroke.

Category	Symptoms/signs	Details
General Symptoms (21)	Lethargy, apnea, hypotonia	Nonspecific symptoms that may present in the acute phase of infantile strokes.
Perinatal Strokes (21)	Focal seizures, lethargy	Occur within the first days after birth; visible neurological deficits may appear weeks or months later.
Young Infants (21)	Decreased oral intake, respiratory distress, irritability, bulging fontanelle	Common presentations for infantile strokes. Physical exam may show dilated scalp veins or eyelid swelling.
Toddlers (21)	Increased crying, sleepiness, irritability, feeding difficulties, vomiting, sepsis-like symptoms	Symptoms include cold extremities and may mimic sepsis.
Venous Sinus Thrombosis (21)	Fever, lethargy, dilated scalp veins	Common presentation in young infants, with distinct physical signs like dilated scalp veins.
Subarachnoid Haemorrhage (21)	Irritability, bulging fontanelle	Infants may present with irritability and bulging fontanelle; older children may complain of acute headaches or neck pain.
Focal Neurological Deficits (21)	Hemiparesis, dysphasia/aphasia, hemianopsia, ataxia, headaches	Hemiparesis, dysphasia/aphasia, and hemianopsia suggest supratentorial involvement. Ataxia is typical of infratentorial strokes. Headaches are present in 30% of children and may mimic conditions like hemiplegic migraine or arterial dissection.
Seizures (21)	Occur in 20-48% of cases	More common within the first 24 hours of stroke. Early seizures portend a higher risk of developing epilepsy within 6 months.
Paediatric Ischemic Strokes (22)	Hemiplegia with upper limb predominance	The majority of paediatric ischemic strokes occur in the middle cerebral artery distribution, often leading to hemiplegia, with the upper limb being more affected.

4. Investigations

Infantile stroke, although less common than in adults, presents significant challenges due to its varied and often nonspecific symptoms. Effective early recognition relies on tools adapted from adult practices, such as the FAST and beFAST tests, with additional attention to age-specific signs like seizures and headaches. Diagnosis hinges on advanced imaging techniques, primarily MRI, which offers the best sensitivity for detecting and characterizing strokes in children. However, CT scans and other imaging modalities also play crucial roles, especially in emergency settings. In order to prevent radiation and contrast exposure in children, paediatric acute ischaemic stroke (AIS) frequently calls for quick and accurate diagnostic procedures. In emergency situations, developing imaging techniques tailored to paediatric patients is essential for prompt and precise diagnosis [2, 23].

Stroke-like episodes are often better visualized using multimodal MRI, which can reveal vasogenic edema and potentially cytotoxic components. Acute perfusion studies may indicate hyperperfusion during stroke-like lesions. For patients with conditions that predispose them to strokes, such as mitochondrial disorders or other metabolic errors, close monitoring during acute decompensation events is essential [1]. Digital subtraction angiography remains the gold standard. PCA dissections generally have a more benign clinical course and prognosis compared to other intracranial dissections [24]. According to a case study done by Kamal Phelps the effectiveness in diagnosis streamlined the decision-making process, as urgent magnetic resonance imaging (MRI) enabled the stroke team to quickly identify and dismiss stroke mimics. Despite concerns that MRI might be delayed due to the need for anesthesia, the use of a fast sequence MRI minimized the need for sedation, with only 7 out of 40 patients requiring it [3].

Children who have experienced a stroke should undergo neurovascular imaging as soon as possible. Vascular imaging, particularly with MRA, can help identify arteriovenous malformations (AVMs) or cavernomas that might be responsible for cerebral hemorrhage. If no other cause for the hemorrhage is identified, conventional catheter-based angiography, although invasive, should be considered. Treatment decisions should be made on a case-by-case basis by a multidisciplinary team that includes a neurologist, pediatric neurologist, and neuroradiologist [25].

5. Management

The management of AIS in children requires a nuanced understanding of both the potential benefits and risks associated with treatments like rt-PA and mechanical thrombectomy. While current protocols are largely derived from adult studies, the unique characteristics of pediatric strokes necessitate ongoing research, and the establishment of evidence-based guidelines tailored for children. The successful outcomes in the presented cases, despite initial treatment failures, highlight the importance of rapid intervention and the need for specialized care in pediatric stroke management [21].

The primary goal of treating pediatric stroke is to protect the developing brain by minimizing acute injury and preventing neurodevelopmental impairments. Due to the lack of robust pediatric-specific data, treatment often relies on extrapolated guidelines from adult studies, such as those from the Canadian Best Practice Guidelines and the American Heart Association.

Continuous monitoring in a clinical unit is recommended, with intensive care transfer for select cases. Antithrombotic treatment is generally advised but must be preceded by the exclusion of hemorrhagic stroke. While anticoagulant therapy remains controversial, guidelines suggest using unfractionated heparin or low molecular-weight heparin for certain conditions,

while aspirin is often recommended for secondary prevention in children not at high risk for recurrent embolism [26]. Surgical interventions may be necessary for specific causes, such as cardioembolic strokes. Supportive care is crucial, focusing on optimizing physiological parameters and preventing secondary brain injury. Rehabilitation is vital for improving long-term outcomes, emphasizing a multidisciplinary approach that considers both the child's and families' emotional well-being [26]. Overall, while preliminary studies indicate potential safety for anticoagulation in pediatric stroke, further randomized trials are needed to establish optimal treatment protocols.

Guidelines currently do not support the use of thrombolysis with tissue plasminogen activator (t-PA) or mechanical thrombectomy in children outside specific research protocols due to insufficient evidence of safety and efficacy. Despite this, some pediatric patients with acute ischemic stroke (AIS) have been treated with these methods based on limited case reports and extrapolation from adult studies [26]. Approximately 2% of children with AIS in the U.S. receive intravenous thrombolysis, while intra-arterial thrombolysis has been successfully utilized in small cohorts, although no randomized controlled trials exist for this demographic [26]. Mechanical thrombectomy has also been applied to select pediatric patients, particularly those with large intracranial artery occlusions, but guidelines caution against its routine use due to the risks associated with adult-sized devices and the unique considerations in treating children [26]. Decision-making for these interventions should consider the severity of neurological deficits, the size of the affected artery, and the experience of the treating center with pediatric stroke cases [26]. Overall, there is a pressing need for safety guidelines and further research to establish effective treatment protocols for pediatric stroke management.

In managing pediatric acute ischemic stroke (AIS), aspirin is generally recommended for secondary stroke prevention in children who are not at high risk for recurrent embolism and do not have hypercoagulable disorders, with dosages ranging from 1 to 5 mg/kg daily [26]. The optimal duration of therapy is not well-defined, but a minimum of two years is suggested, while the risk of Reye's syndrome should be considered. Alternatives like clopidogrel may be used if aspirin is not tolerated. Anticoagulation with low molecular weight heparin or warfarin is advised for children with cardioembolic strokes or extracranial arterial dissections, although the comparison of antiplatelet versus anticoagulant therapies remains controversial and requires further randomized trials [26]. For specific conditions such as sickle cell disease, management includes multidisciplinary evaluation and regular blood transfusions, while metabolic diseases necessitate correcting the underlying defects. Surgical interventions may be necessary in cases of moyamoya disease or cardioembolic causes. Supportive care is essential, focusing on optimizing physiological parameters and preventing secondary brain injury, while rehabilitation involving a multidisciplinary team is crucial for improving long-term outcomes, leveraging the brain's plasticity in children [26].

Supportive care for pediatric acute ischemic stroke focuses on optimizing physiological parameters like glycemia, volemia, oxygenation, and blood pressure, while preventing and treating hyperthermia and infections [26]. Seizures are controlled with antiepileptic medications and continuous EEG monitoring if needed. Oxygen supplementation is only provided for hypoxemia, and hypothermia has not shown benefits. Blood pressure is cautiously reduced by up to 25% in the first 24 hours for extreme elevations, avoiding excessive lowering. Intracranial hypertension may warrant hyperventilation, osmotic agents, or neurosurgical interventions like hydrocephalus drainage or decompressive craniectomy [26]. Rehabilitation is crucial, leveraging brain plasticity with a multidisciplinary team utilizing a biopsychosocial model, considering the family's emotional well-being. Adjunctive therapies like constraint-induced movement therapy, bimanual training, and transcranial magnetic stimulation show promise, with the greatest benefits seen during early development and hopeful improvements in long-term motor outcomes [26].

The TIPS study aimed to address critical concerns regarding the safety and efficacy of tissue plasminogen activator (tPA) in treating acute arterial ischemic stroke (AIS) in children aged 2 to 17 years [27]. Despite the rigorous design and preparation involving extensive collaboration among pediatric and adult stroke specialists, the study faced significant recruitment challenges, enrolling only one patient out of 93 screened. This low enrollment highlights the complexities of diagnosing and treating pediatric strokes within the therapeutic window, as many potential candidates were excluded due to contraindications or alternative diagnoses. Nonetheless, the TIPS study contributed valuable insights into the management of pediatric stroke, establishing safety protocols and dosing guidelines for tPA, which may help inform future clinical practices and trials. The findings suggest that while the risk of symptomatic intracranial hemorrhage in children treated with tPA is low, further research and the establishment of dedicated pediatric stroke centers are essential for improving outcomes and expanding treatment options for this vulnerable population [27].

The TIPS study aimed to establish a safe and effective dosing regimen for tissue plasminogen activator (tPA) in treating acute ischemic stroke (AIS) in children, focusing on dose-limiting toxicity (DLT) defined by specific hemorrhagic events within 36 hours of administration. The study utilized a Bayesian approach to determine the maximal tolerated dose (MTD) across two age strata (2-10 years and 11-17 years), with an acceptable DLT target set at 10%. Despite the rigorous design, the study faced significant challenges in patient recruitment, with only one child enrolled out of 93 screened, primarily due to contraindications and alternative diagnoses.

This low enrollment underscores the complexities of pediatric stroke management, including the need for rapid diagnosis and treatment within a narrow therapeutic window. Significant challenges were encountered, including delays in human subjects' approval, costs for tPA storage and sample processing, and lack of dedicated research coordinators [27].

Out of the 93 children screened, only 43 were confirmed to have AIS, while the remainder presented with stroke mimics or contraindications to tPA treatment. The study was ultimately closed by the National Institute of Neurological Disorders and Stroke (NINDS) due to insufficient patient enrollment, highlighting the rarity of pediatric AIS and the need for improved recognition and referral protocols to ensure timely treatment within the narrow therapeutic window. Although the TIPS study, though unsuccessful in reaching its enrollment goals, provided valuable insights into the challenges of conducting acute stroke trials in children and laid the groundwork for future research in this field [27].

The preparation for the TIPS trial has significantly enhanced the readiness of pediatric stroke centers (PPSCs) across North America to effectively identify, diagnose, and treat acute childhood strokes. Following the initiation of the trial, there was a marked increase in the establishment of pediatric-specific stroke teams, urgent neuroimaging capabilities, and streamlined stroke pathways in emergency departments and intensive care units [28]. Although many sites had access to subspecialists since 2004, the infrastructure for rapid stroke treatment was not robust until the TIPS trial funding in 2010 catalyzed development. The trial also fostered collaboration among various clinical services, leading to the creation of comprehensive stroke protocols and order sets, which took considerable time and resources to implement. Importantly, most TIPS sites have met the primary criteria for adult primary stroke centers, establishing valuable relationships with adult stroke teams to enhance pediatric care. Despite the unique challenges presented by pediatric stroke, including different pathogenesis and risk factors, the TIPS trial has laid the groundwork for the future establishment of formal guidelines for PPSCs. This initiative is crucial for creating regional centers capable of managing pediatric strokes with the same urgency and standards of care as adult centers, ultimately improving outcomes for children experiencing acute arterial ischemic strokes [28].

The results of recent studies suggest that endovascular thrombectomy is a feasible and safe treatment option for children with acute ischemic stroke due to large vessel occlusion, with outcomes comparable to those seen in adult trials [29]. In the largest study to date, the Save Child's study, 73 children underwent successful recanalization with few complications, including a 1% rate of symptomatic intracranial hemorrhage. Most patients showed significant neurological improvement, with median modified Rankin Scale scores of 1 at both 6 and 24 months. However, outcomes were worse in younger children aged 0-6 years. Limitations include the retrospective design, lack of a control group, and heterogeneity in inclusion criteria across centers. Although randomized trials would be ideal, they are unlikely given the rarity of pediatric stroke and strong evidence supporting thrombectomy in adults. Careful patient selection is important, considering factors like stroke severity, vessel size, and underlying arteriopathies. Establishing dedicated pediatric stroke centers with multidisciplinary expertise is crucial to optimizing outcomes. Overall, these findings support the use of thrombectomy in carefully selected children with large vessel occlusion, while emphasizing the need for further research to refine patient selection and treatment protocols [29].

When managing pediatric strokes, physicians should be aware of several key differences from adult strokes that can assist in diagnosis and treatment: Pediatric strokes often present with atypical or diffuse symptoms, such as only a headache, seizure, or a lack of clear clinical signs. Non-atherosclerotic arteriopathies, hematological disorders, and coagulopathies play a more significant etiological role in pediatric strokes, while atherothrombotic causes are more common in adults. Pediatric ischemic strokes frequently involve multiple coexisting risk factors. Nontraumatic, spontaneous intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), and subarachnoid hemorrhage (SAH) in children are caused by structural lesions in up to 85% of cases. Evaluating for thrombophilia is beneficial in every case of pediatric stroke [25].

Analysing multiple genotype combinations is a more effective approach for patient stratification [30]. This approach will enhance individualized stroke prevention, neuroprotection, and tailored secondary prevention strategies. This review emphasizes the need for a comprehensive view of pediatric stroke, considering all genetic aspects—monogenic, polygenic, risk factors, and modifiers—to avoid overlooking important elements. Given the multi-factorial nature and various subtypes of pediatric stroke, each genetic variant or combination of variants could be crucial for drug discovery and have a significant impact on treatment for infants and children [30].

Based on discussions from a UK-based online stroke community, several key factors influence recovery from pediatric stroke. First, early intervention and treatment play a crucial role in improving outcomes, as timely access to therapies like clot-dissolving medications or surgery can minimize brain damage [18]. Access to rehabilitation services, such as physiotherapy, speech therapy, and occupational therapy, is essential for restoring function and improving the child's quality of life. Parental and caregiver involvement is another significant factor. Engaged and informed caregivers often provide essential support, motivation, and advocacy for their child's recovery process [18]. Younger children may have more plasticity in their brain, potentially aiding recovery, but

may also face developmental challenges as they grow. Lastly, ongoing research and awareness in pediatric stroke are vital in shaping the recovery landscape. As this area of medicine continues to evolve, new treatments and approaches may improve long-term recovery prospects for children who have experienced a stroke [18].

Ruptured cerebral arteriovenous malformation was the most common cause of PHS and sudden onset of severe headache was the key presenting symptom. Prompt surgical intervention for PHS reduced the rebleeding rate [31]. Non-pharmacological interventions also play a crucial role in improving cognitive outcomes in children with ischemic stroke. Early rehabilitation, including cognitive therapy, speech therapy, and occupational therapy, is vital in helping children regain lost functions or develop compensatory strategies. Cognitive therapy focuses on improving specific areas of cognition, such as memory, problem-solving, and attention, while speech and occupational therapies address communication and daily living skills. Educational support and environmental modifications also contribute to better cognitive outcomes. Specialized educational programs tailored to the child's needs, such as individualized education plans (IEPs), can help manage learning challenges [32].

Surgical revascularization is emphasized as a crucial intervention to enhance cerebral blood flow and improve long-term outcomes, as conservative management has been linked to poor intellectual development [33]. The synthesis of global stroke guidelines by the World Stroke Organization (WSO) underscores the importance of comprehensive, accessible, and specific guidelines for effective stroke care. Applying this to infantile stroke, it is evident that there is a critical need for tailored guidelines that address the unique aspects of stroke in infants and children. These guidelines should encompass acute care, secondary prevention, and rehabilitation, with strong recommendations for timely reperfusion therapies, management of congenital and acquired risk factors, and multidisciplinary rehabilitation [34].

6. Prognosis

In children, stroke recurrence is frequent and contributes significantly to both morbidity and mortality. The five-year recurrence rates are estimated to range from 6% to 20%, with some subgroups experiencing rates as high as 66%. Research has highlighted vasculopathy, especially moyamoya disease, as a significant predictor of recurrent stroke. Additionally, early evidence suggests that prothrombotic states may also increase the risk of recurrence, although many of these studies are limited by their size and scope [35].

In most cases (75%), recurrent strokes affected the same vascular territory as the initial arterial ischemic stroke (AIS). Specifically, 62.5% of the recurrences were in the anterior circulation, while 37.5% involve the posterior circulation [35]. Particularly in cases involving spontaneous venous thromboembolism (VTE) and cerebral Sino venous thrombosis (CSVT), is a critical area of concern due to the significant morbidity associated with these conditions. Research indicates that approximately 40% of infants with cerebral thrombosis who undergo long-term neurological follow-up experience moderate to severe neurologic sequelae, as classified by the Paediatric Stroke Outcome Measure Severity Classification Scheme (PSOM-SCS) [36].

This high rate of adverse outcomes underscores the importance of ongoing monitoring and tailored care for affected infants to address potential long-term neurological issues. The findings also highlight the necessity for comprehensive assessments of non-thrombotic outcomes in future studies, which will help in fully understanding the impact of paediatric VTE on neurological health [37]. Overlooked but significant cause of morbidity and mortality in younger individuals is paediatric stroke. Although rare compared to adult stroke, it is one of the leading causes of severe neurological injury in children and ranks among the top 10 causes of childhood death [38].

Recent studies have suggested, though not conclusively, that timely revascularization through mechanical embolectomy may improve outcomes in large-vessel acute ischemic stroke (LVPAIS) [39]. However, these findings should be approached with caution due to the lack of a control group. For severe cases involving life-threatening cerebral oedema, decompressive craniectomy (DCH) might be a critical, potentially life-saving treatment. Although recommendations for DCH are based on limited case studies and reports, it is crucial to note that malignant stroke patients not responding to medical treatment generally have a poor prognosis. Without prospective studies to confirm the benefits of decompressive craniectomy, its effectiveness for malignant cerebral infarction in paediatric patients remains uncertain [39].

In the case of neonatal haemorrhagic stroke (NHS) is concerning, as research indicates that approximately 44% of affected infants experience poor neurological outcomes. Follow-up studies reveal that many survivors face significant long-term challenges, emphasizing the necessity for early diagnosis, comprehensive management, and tailored rehabilitation strategies to address the unique needs of these vulnerable patients and improve their quality of life [4]. The collaborative efforts fostered by the TIPS trial have laid a foundation for more effective treatment strategies, ultimately aiming to enhance outcomes for children suffering from acute arterial ischemic strokes. However, continued focus on tailored rehabilitation and long-term follow-up is crucial to address potential neurological deficits that may arise from these conditions [28].

Recovery from infantile stroke is significantly influenced by several key factors. Early intervention and treatment are critical; timely access to therapies such as clot-dissolving medications or surgical options can greatly reduce brain

damage and improve outcomes. Access to comprehensive rehabilitation services—including physiotherapy, speech therapy, and occupational therapy—is essential for helping children regain function and enhance their quality of life. Additionally, the involvement of parents and caregivers plays a vital role in the recovery process. Engaged caregivers provide crucial support, motivation, and advocacy, which can positively impact the child's rehabilitation journey. Overall, a coordinated approach that emphasizes early treatment, effective rehabilitation, and active caregiver participation is fundamental for optimizing recovery from infantile stroke.

Additionally, age at the time of stroke and the specific area of the brain affected can heavily influence recovery outcomes. Younger children may have more plasticity in their brain, potentially aiding recovery, but may also face developmental challenges as they grow. Lastly, ongoing research and awareness in paediatric stroke are vital in shaping the recovery landscape. As this area of medicine continues to evolve, new treatments and approaches may improve long-term recovery prospects for children who have experienced a stroke [18].

Timely identification of symptoms and imaging is essential to minimize complications like increased intracranial pressure and further brain damage. The study likely highlights the importance of surgical or medical interventions, such as decompression or controlling the underlying cause of the bleed, in stabilizing patients. The extent of brain injury, location of the bleed, and rapidity of medical intervention are key factors determining recovery. The case series might show that younger patients have better recovery potential due to brain plasticity, but this is not guaranteed, and long-term follow-up and rehabilitation are often required [31].

Additionally, the case series may highlight the challenges of managing paediatric haemorrhagic stroke in a healthcare system where resources or specialized paediatric stroke units may be limited. This underscores the importance of training, early referral to specialist care, and the need for multidisciplinary teams in managing these complex cases [31].

In the analysis of the distribution of risk factors for ischemic stroke in Chinese young adults and its correlation with prognosis, unique risk factors and their prevalence in this population shape both the occurrence and outcomes of ischemic stroke. Unlike older adults, where hypertension and atherosclerosis dominate, young adults in China often present with a different profile, including congenital heart disease, lifestyle factors, metabolic disorders, and specific genetic disorders.

Lifestyle factors, including diet, smoking, and alcohol consumption, have been found to significantly influence stroke risk in this group. Genetic factors, such as family history of cardiovascular disease, may also play a notable role. Additionally, conditions like hypercoagulability or autoimmune diseases may be disproportionately prevalent in this younger demographic. Young adults tend to have better recovery potential than older adults, owing to greater brain plasticity and fewer coexisting health issues. However, the presence of multiple risk factors, particularly those that are not well-controlled or modifiable (e.g., congenital or genetic conditions), correlates with poorer outcomes and a higher likelihood of recurrent stroke. Timely medical intervention and post-stroke rehabilitation are crucial for improving prognosis. Younger patients who receive early treatment, particularly thrombolysis or mechanical thrombectomy, may recover more fully [19].

Non-pharmacological interventions play a crucial role in improving cognitive outcomes in children with ischemic stroke. Early rehabilitation, including cognitive therapy, speech therapy, and occupational therapy, is vital in helping children regain lost functions or develop compensatory strategies. Cognitive therapy focuses on improving specific areas of cognition, such as memory, problem-solving, and attention, while speech and occupational therapies address communication and daily living skills. Educational support and environmental modifications also contribute to better cognitive outcomes. Specialized educational programs tailored to the child's needs, such as individualized education plans (IEPs), can help manage learning challenges [32].

Given that the visual pathway occupies a large portion of the brain, it's significant that 5 out of 23 children with strokes exhibited notable visual impairments. In children, ischemic strokes often affect the anterior cerebral circulation, and visual field defects may go unnoticed, especially if not associated with spatial neglect. Cerebral Visual Impairment (CVI) can cause severe visual difficulties even if visual acuity seems normal, which is particularly challenging for young children who may not be able to articulate their visual problems. There is a pressing need for further research to improve understanding, diagnosis, and treatment of CVI, which will help prevent secondary developmental issues related to visual impairments following a stroke [40].

Most children who experience paediatric stroke exhibit resilience, with 74% achieving good cognitive outcomes within 12 months post-stroke. Static factors, such as age at stroke and lesion characteristics, play a more significant role in determining cognitive recovery compared to dynamic factors like socioeconomic status and parental function. Notably, children with better acute neurological and adaptive skills tend to have improved cognitive trajectories, while those with more extensive brain involvement and seizure history are at greater risk for cognitive decline. These findings highlight the importance of early identification and intervention for vulnerable children to optimize recovery and support long-term cognitive development [41].

Arterial ischemic stroke (AIS) in children, with an incidence of 1.3 to 1.6 per 100,000 annually in developed countries and leads to significant long-term neurological

deficits and recurrent strokes. The absence of traditional adult stroke risk factors complicates paediatric stroke management, as demonstrated by recruitment challenges in trials like the halted TIPS trial for intravenous thrombolysis. Emerging evidence from studies such as the Save ChildS Study supports the safety and efficacy of mechanical thrombectomy (MT) in children, although limitations necessitate further investigation. To address ethical concerns and gather comprehensive data, the Save ChildS Pro registry has been proposed to evaluate MT outcomes and establish selection criteria for vulnerable paediatric subgroups. This initiative is essential for improving clinical outcomes in childhood stroke [42].

CONCLUSION

Paediatric stroke, although less common than in adults, poses serious health risks, with an incidence of 2.5 to 13 per 100,000 children annually and mortality rates of 10% to 25%, especially for haemorrhagic strokes. Unique physiological differences complicate diagnosis and management, as children may present with vague symptoms like seizures rather than classic signs. Advanced imaging techniques such as MRI are crucial for timely diagnosis, while treatment often follows adult guidelines but must be tailored to children's specific needs. Emerging therapies like tPA and mechanical thrombectomy show promise but require further research. Early intervention and specialized rehabilitation are vital due to high recurrence rates in this population, underscoring the need for dedicated paediatric stroke centres and ongoing research to improve outcomes for affected children and their families.

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