

# Rare Genetic Risk Factors of Neuropsychiatric Disorders in Children

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## Description

Key elements of the pediatric stroke protocol should include recognition tools, stroke alert mechanism, stroke order sets, timely imaging, laboratory evaluation, and treatment options. Substantial advancements have been made in the field of pediatric stroke protocols mainly due to formation of international consortiums and clinical trial. Despite significant progress, treatment options remain controversial. The aetiologies of arterial ischaemic stroke in children are diverse and often multifactorial. A large proportion occurs in children with cardiac disorders. We hypothesized that the clinical and radiographic features of children with arterial ischaemic stroke attributed to cardiac disorders would differ from those with other causes. Using the large population collected in the prospective International Paediatric Stroke Study, we analysed the characteristics, clinical presentations, imaging findings, and early outcomes of children with and without cardiac disorders. Analysis of imaging data identified significant differences in the vascular distribution (anterior vs. posterior circulation or both) between groups. Bilateral strokes and haemorrhagic conversion were more prevalent in the cardiac disorders group.

## Perinatal Stroke

Perinatal stroke has become increasingly recognized, but the incidence is probably underestimated because of variation in the presentation, evaluation, and diagnosis. Based on estimates from population-based studies of infants with seizures, perinatal stroke occurs in approximately 1 in 4000 term births. Most perinatal strokes involve the middle cerebral artery and are caused by thromboembolism from an intracranial or extra cranial vessel, the heart, or the placenta. Cardiac disorders, coagulation abnormalities, and infection are risk factors for stroke in the perinatal period. This article discusses the epidemiology of ischemic stroke occurring in the perinatal and neonatal period, including cerebrovascular events that are diagnosed during the perinatal period and those diagnosed retrospectively, when evidence of hemiparesis or post neonatal seizures leads to later evaluation and neuroimaging. Paediatric stroke is relatively rare, with approximately 1000 childhood strokes in the United States per year. However, the occurrence of stroke in children leads to significant morbidity and mortality, warranting the development proven screening tools, protocols,

and treatment options. Because significant delays in seeking medical attention can occur, time to recognition of paediatric stroke in the emergency department is uniquely challenging and critical. Once recognized, a trained multidisciplinary team with a multifaceted approach is needed to provide the best possible outcome for the patient.

## Genetic Predisposition

Cardiac disorders were identified in almost one-third of children with arterial ischaemic stroke. They had similar clinical presentations to those without cardiac disorders but differed in age and headache prevalence. Children with cardiac disorders more frequently had a 'cardioembolic stroke pattern' with a higher prevalence of bilateral strokes in both the anterior and posterior circulations, and a greater tendency to haemorrhagic transformation. Understanding the vascular injury pathway is crucial to developing rational strategies for secondary stroke prevention in children. Laboratory assays include serologies (acute and convalescent) and molecular assays for herpesviruses and levels of inflammatory markers. Participants are followed prospectively for recurrent ischemic events (minimum of 1 year). The analyses will measure association between markers of infection and cerebral arteriopathy and will assess whether cerebral arteriopathy and inflammatory markers predict recurrent stroke. Stroke was once recognized so infrequently in children that it was considered a medical curiosity, and until relatively recently, our understanding of the nature of cerebrovascular disorders in children was somewhat rudimentary. However, we now know that cerebrovascular disorders are relatively common among children, 1 and with the advent of less-invasive diagnostic studies and more targeted treatments, stroke is now recognized as a very important clinical condition in children. Risk factors for stroke in adults include hypertension, diabetes, and smoking, as well as cardiac disease and sickle cell anemia; asymptomatic cerebrovascular disease and transient ischemic events may predict stroke in this age group. The investigation of a child with a stroke has traditionally focused on finding a single cause rather than looking for risk factors to which the patient may be exposed lifelong. Approximately half of children presenting with stroke have a known predisposing condition, but some have unexpected pathologies such as primary cerebrovascular disease associated with congenital heart anomalies, or may have modifiable risk

factors such as hypertension associated with sickle cell disease. The literature on children presenting with initially unexplained (cryptogenic) stroke suggests that there is a daunting list of possible causes, but since the series have mainly been small, it has been difficult to evaluate the relative importance of the reported associations. This paper reviews the literature on congenital, genetic, and acquired risk factors for stroke in childhood, and includes data from the large series of patients seen at Great Ormond Street Hospital over the past 10 years. The majority has arteriography abnormalities and there is little evidence for asymptomatic cardiac disease. Genetic predisposition, trauma, infection, and nutritional deficiencies appear to be important, although case-control studies will be required to prove causation. Appropriate screening for modifiable risk factors may lead to prevention of recurrence in some patients. Strokes associated with congenital heart disease

or vasculopathy cost the most, while perinatal or idiopathic strokes cost the least. Higher costs are correlated with worse impairment and poorer quality of life. Stroke etiology significantly influences the cost of pediatric stroke. Future cost-benefit studies must consider etiology when estimating the incremental costs associated with stroke. For children requiring mechanical circulatory support as a bridge to cardiac transplantation in North America, options previously were limited to extracorporeal membrane oxygenation. There was one late death nearly 2 years after transplant. Complications included stroke in seven patients, two of which were ultimately fatal. Five patients required re-operations for bleeding or evacuation of hematoma. Despite a disappointing rate of neurologic morbidity, our preliminary experience with the EXCOR has been very encouraging.