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Topical Review

Stroke in Children With Cardiac Disease: Report From the International Pediatric Stroke Study Group Symposium



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ABSTRACT

BACKGROUND: Cardiac disease is a leading cause of stroke in children, yet limited data support the current stroke prevention and treatment recommendations. A multidisciplinary panel of clinicians was convened in February 2014 by the International Pediatric Stroke Study group to identify knowledge gaps and prioritize clinical research efforts for children with cardiac disease and stroke. **RESULTS:** Significant knowledge gaps exist, including a lack of data on stroke incidence, predictors, primary and secondary stroke prevention, hyperacute treatment, and outcome in children with cardiac disease. Commonly used diagnostic techniques including brain computed tomography and ultrasound have low rates of stroke detection, and diagnosis is frequently delayed. The challenges of

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research studies in this population include epidemiologic barriers to research such as small patient numbers, heterogeneity of cardiac disease, and coexistence of multiple risk factors. Based on stroke burden and study feasibility, studies involving mechanical circulatory support, single ventricle patients, early stroke detection strategies, and understanding secondary stroke risk factors and prevention are the highest research priorities over the next 5–10 years. The development of large-scale multicenter and multispecialty collaborative research is a critical next step. The designation of centers of expertise will assist in clinical care and research. **CONCLUSIONS:** There is an urgent need for additional research to improve the quality of evidence in guideline recommendations for cardiogenic stroke in children. Although significant barriers to clinical research exist, multicenter and multi-specialty collaboration is an important step toward advancing clinical care and research for children with cardiac disease and stroke.

Keywords: cardiac, stroke, arterial ischemic, congenital heart disease

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Introduction

Children with congenital and acquired cardiac disease are at an increased risk of arterial ischemic stroke (AIS). The risk varies depending on age, comorbidities, underlying cardiac diagnosis, and factors that can vary over time, including changing hemodynamics, new cardiac procedures, and/or the need for mechanical circulatory support devices. Children with particular cardiac lesions, such as single ventricle physiology and cardiomyopathy appear to be at greater risk. In spite of the increased risk of stroke in children with heart disease, diagnosis is frequently delayed, and high-level evidence on prevention and treatment of stroke in this group is lacking. In combination with other factors that influence neurological outcome, including other cardiac-related brain injury, stroke in this population leads to significant morbidity and mortality. The International Pediatric Stroke Study group organized a symposium in 2014, comprising pediatric subspecialists in neurology, cardiology, hematology, and critical care medicine, to address stroke in this vulnerable population. The aims of the meeting were as follows: to foster multidisciplinary collaboration, to review current knowledge, to identify important gaps in knowledge, and to outline priorities for further research. This report summarizes the findings and recommendations from the symposium.

Current knowledge and knowledge gaps

Incidence

Stroke has been associated with both congenital and acquired heart disease in children. Congenital heart disease occurs in 4–10 per 1000 live births.¹ Approximately 85% of patients survive into adult life and within this decade, in North America, approximately 1 in 150 adults are expected to have some form of congenital heart disease.² Although stroke has been associated with most types of cardiac disease, those with cyanotic and complex congenital heart disease appear to be at greatest risk.

Reported incidence rates for stroke in children with cardiac disease are primarily based on single- or dual-center studies. These data are summarized in [Table 1](#). There is considerable variability in reported rates, and caution should be used when interpreting studies because of limitations related to small sample size, non-population-based data, variable stroke definitions, ascertainment bias,

and variability in the definition of cardiac disease. Also as indicated in the table, some studies considered AIS independently, whereas others looked at combined rates of AIS and other neurological injury such as hemorrhagic stroke and cerebral sinovenous thrombosis.

Hoffman et al.³ estimated the overall incidence of AIS in children with cardiac disease based on a cohort in the Intermountain Pediatric Stroke Database, United States. Their reported incidence rate was 132 of 100,000 per year, which is dramatically higher than the general incidence of AIS in children of 2–8 of 100,000 per year.^{4–6} Among cohorts of neonates and children with AIS, the prevalence of cardiac disease ranges from 10%–31%^{6–13}; however, studies varied as to whether they included isolated patent foramen ovale (PFO) as a cardiac disease. In the vast majority of patients, cardiac disease is known before the onset of stroke. In the International Pediatric Stroke Study cohort, Dowling et al.¹³ found that children with cardiac disease and AIS tended to be younger at presentation and were more likely to have strokes in a “cardioembolic stroke pattern,” defined as strokes that were multiple, bilateral, and involved both the anterior and posterior circulations, compared with those with AIS and no cardiac disease. A higher rate of hemorrhagic transformation was also seen in those with AIS and cardiac disease.¹⁴ The increased rate of hemorrhagic transformation may be related to the underlying embolic mechanism or the greater prevalence of anticoagulation therapy at the time of stroke in children with cardiac disease.

Children with mechanical circulatory support devices including extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) are at particularly high risk of stroke. Neurological dysfunction, most commonly ischemic stroke, occurred in 29% and was the leading cause of death or withdrawal of care in the pediatric Berlin Heart EXCOR trial.^{15,16} Comparison of VAD-supported patients versus ECMO-supported patients requires caution. Published data on stroke prevalence in ECMO cohorts (including the ECMO comparator group in the Berlin EXCOR VAD cohort) come from the Extracorporeal Life Support Organization registry, which is based on voluntary reporting from centers with widely varying approaches to diagnosis and classification of events, and without central adjudication. The published data on stroke prevalence in the Berlin Heart EXCOR VAD cohort are more reliable because neurological event ascertainment was mandated,

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