Risk Factors for Childhood Stroke: Little Folks Have Different Strokes!

In the current issue, Ganesan and colleagues present comprehensive data on stroke risk factors in a large, well-defined consecutive cohort of children with arterial ischemic stroke. Ischemic stroke in childhood is emerging as a serious, frequent, and underrecognized disorder, affecting at least 7 per 100,000 children per year. There have been no randomized, clinical trials of acute or secondary preventative therapies in childhood stroke. Yet, outcomes in affected children include neurological deficits or seizures in approximately two thirds and recurrent events in 10 to 25%. Because these outcomes are lifelong, the burden of illness impacts affected individuals over many decades. Adverse outcomes are closely linked to the type and number of underlying risk factors emphasizing the importance of searching for these factors.

The nature of, and approach to, stroke risk factors in children differs fundamentally from adults. In children, a more direct cause–effect relationship between risk factors and stroke events exists, in comparison with adults, in whom risk factors such as smoking, obesity, hypertension, and diabetes cause stroke indirectly via the acceleration of atherosclerosis. In addition, age-related differences in cerebrovascular and coagulation systems limit the direct extrapolation of research from adults with stroke to children. Age-specific research is necessary.

The understanding of risk factors in childhood stroke is important for several reasons. First, there is a myriad of risk factors associated with childhood stroke. Given the high cost, intricacy, and potential complications of testing for these factors, an evidence-based approach to selective testing is paramount. Second, outcomes and treatments vary across risk factor categories, necessitating that relevant risk factors be defined and incorporated into the design of stroke trials in children. Third, the absence of atherosclerosis in children facilitates the identification of other risk factors, including prothrombotic disorders which may contribute to the pathogenesis of adult stroke.

Ganesan and colleagues utilized a novel approach, comparing risk factors in “cryptogenic” stroke to those in “symptomatic” stroke. In children with cryptogenic stroke, abnormal investigations were found in the majority but included nonspecific findings such as arterial occlusion and hypoplasia. Idiopathic strokes typically represent 25% of children with stroke, indicating the need for additional research.

The Ganesan study found prothrombotic disorders relatively infrequently compared with previous reports. However, iron deficiency anemia, a treatable risk factor for childhood stroke, was present in nearly one quarter of the children studied. Cardiac disease was present in 28% of the children. The authors question the utility of echocardiography in previously healthy children because only 7 of 103 children with cryptogenic stroke had abnormal studies. However, if the subclinical abnormalities influence the risk of recurrent stroke, and are treatable, their detection even at such rates may be important.

Nearly 90% of children in the Ganesan study underwent vascular imaging, of whom 59% had a clear vasculopathy. The remaining 41% had normal vasculature, vascular occlusion, or hypoplastic arteries. This study confirms the importance and the unique features of cerebral vasculopathy in children compared with adults. In children, vasculopathy is usually unilateral, located within the terminal internal carotid artery, or proximal segments of the middle or anterior cerebral arteries, and is referred to as transient cerebral arteriopathy of childhood, or, if chicken pox precedes the stroke, postvaricella angiopathy. In contrast with adult vasculopathies and with childhood moyamoya, childhood vasculopathies are nonprogressive and represent a monophasic attack on the arterial wall, by either varicella or other as yet unknown causes. Despite the transient nature of the focal arteriopathies, the important risk of early recurrent stroke underlines the need for further study of their pathophysiology, as well as the development of more aggressive therapies.

In the Ganesan study, hypertension was strongly associated with vascular disease. In a case–control study in progress at our center, we also have found this association in both children with stroke and in disease controls, children with epilepsy from the same clinic suggesting anxiety as an underlying cause. As emphasized by the authors of the Ganesan study, in the setting of vasculopathy, hypertension likely represents a compensatory response for increasing cerebral perfusion pressure and is unlikely to be a risk factor for childhood stroke.

In this and other studies, children with known risk factors including cardiac disease also were found to have unsuspected vasculopathy or other additional risk factors, emphasizing the importance of searching for multiple risk factors. Data from 460 older infants and children with arterial stroke in the Canadian Registry showed the following breakdown of risk factor categories: none identified in 26%, vascular in 38%, cardiac in 23%, intravascular in 32%, with fully 25% of patients having more than one major mechanism at play. In individual children, both predisposing and
triggering risk factors often act in concert. Prothrombotic disorders are typical predisposing risk factors, which combine with other underlying disorders or triggering events.11–15 Viral infection, dehydration, and cardiac surgery are triggering factors. There is the need for careful delineation of all risk factors in each child with stroke, to plan appropriate treatments and to test family members for heritable disorders.5,6 Therapy, for those triggering risk factors that are transient, should be of short duration, whereas therapy for predisposing factors must be of longer duration.

Case–control and cohort studies such as the Ganesan study, using improved vascular imaging and genetic and other laboratory testing approaches, are resulting in an increased definition of stroke risk factors. The next phase of research will be to evaluate the influence of these risk factors on adverse outcomes including stroke recurrence.7

We are at an early and exciting stage of research into childhood stroke. Multicenter, international, consecutive cohort studies recently have been initiated, which will develop and apply standardized approaches to the diagnosis, investigation for risk factors, treatment, and outcome assessment of children with stroke. These multicenter studies will build on existing studies and will provide significantly increased power to further enhance our understanding of risk factors for childhood stroke. Studies that define risk factors for childhood stroke are providing the opportunity to identify subtle but important risk factors for stroke likely at play in adults. Finally, an improved understanding of risk factors is laying the groundwork for studies to assess stroke therapies aimed at preventing childhood stroke through the modification or reversal of risk factors.

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Nitric Oxide and the Axonal Death Cascade

Axonal degeneration has attracted increasing attention as a component of the pathology of disorders such as multiple sclerosis (MS) and Guillain–Barre syndrome (GBS) that traditionally have been viewed as “demyelinating” diseases and is especially important because it can contribute to the acquisition of permanent (non-remitting) deficits.1–3 Its recognition has focused attention on the following questions. What are the events that trigger axonal degeneration within the central nervous system (CNS) and peripheral nervous system (PNS)? What are the subsequent molecular mechanisms, set into motion by the initial trigger, that lead to axonal loss? Can we stop the deleterious cascade by blocking critical molecules in disease models, thereby protecting axons? And if so, can we translate this to the clinical domain in the form of neuroprotective therapies that will preserve function in humans? An article in this issue by Kapoor and colleagues5 suggests a link between nitric oxide (NO) and subsequent molecular events that previously have been indicted as contributors to irreversible axonal injury and adds to a growing