Stroke in Children

Recognizing Opportunities for Improving Care

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Remarkable progress has been made in the evaluation and treatment of children with stroke over the past 20 years. Although the diversity of stroke causes and risk factors in children makes studies challenging, several clinical trials have been completed in children with sickle cell disease that have reduced the rate of stroke (primary prevention)[1–3] and silent cerebral infarct recurrence (secondary prevention).[4] For children with stroke because of other causes, multicenter, international, consecutive cohort studies are in progress that apply standardized approaches to diagnosis, risk factor investigation, treatment, and outcome assessment.[5,6] These multicenter studies will significantly increase our understanding of risk factors for stroke in children and complications of stroke such as seizures and epilepsy. Important single-center studies have focused on stroke pathophysiology and neuromodulation to improve recovery.[7] An increased understanding of stroke mechanisms and outcome lay the groundwork for studies to assess therapies aimed at preventing and lessening the impact of childhood stroke.

In this edition of *Stroke*, leading experts have contributed in-depth reviews on 5 diverse aspects of pediatric stroke: (1) promoting motor skill gains after perinatal stroke with noninvasive neuromodulation, (2) advances in neuroimaging to answer clinical questions regarding the ischemic penumbra, outcome, and rehabilitation potential in pediatric stroke, (3) improvements in pediatric stroke acute care, (4) genetic and environmental causes of cerebral arteriopathy in children, and (5) advances in primary and secondary stroke prevention and the impact of cerebral vasculopathy and cerebral hemodynamics on stroke in children with sickle cell disease. Impressive research has been published in each of these areas within the past few years.

Hinderley et al[8] review noninvasive neuromodulation and rehabilitation to promote motor skill gains in children with hemiparesis after perinatal stroke. Constraint-induced movement therapy involves immobilization of the less-affected upper extremity to compel use of the more-affected limb.[9] In contrast, bimanual training incorporates the more-affected arm into skilled bimanual activities.[10] Potential differences in recovery from a perinatal stroke because of developmental plasticity are intriguing. Motor skill gains after perinatal stroke may occur via advances in constraint-induced movement therapy, bimanual therapy, and noninvasive brain stimulation such as transcranial magnetic stimulation or transcranial direct current stimulation of the motor cortex[7,11]; lessons learned in children with stroke at a young age and high-level of plasticity may inform therapeutic advances in stroke patients of all ages.

Donahue et al[12] review the clinical questions that may be answered with advanced neuroimaging in children with stroke and highlight how quantitative, noninvasive imaging may be used to expand the stroke imaging landscape. New methods that may help differentiate benign oligemia from ischemic penumbra are discussed.[13,14] Emerging and existing imaging modalities that may predict recovery based on functional peri-infarct tissue profiles[15] and allow targeted rehabilitation therapy are reviewed.

Lehmann et al[16] present challenges and opportunities for improving pediatric stroke acute care including decreasing the time to diagnosis via education about stroke symptoms, timely recognition of stroke in the prehospital setting, and availability of rapid neuroimaging. Unfortunately, tools used by emergency medical providers to distinguish adults with stroke have recently been shown to have limited reliability and accuracy in children.[17] Prompt identification of stroke in children offers the opportunity for improved acute care and secondary stroke prevention strategies. Interest in off-label thrombolysis and mechanical thrombectomy has grown, but use of these off-label therapies remains challenging. Careful consideration of risks versus benefits of these recanalization therapies is necessary in children, particularly without pediatric clinical trials. Establishment of pediatric registries to capture safety and efficacy data for stroke reperfusion therapies in children is critical. More importantly, although thrombolysis and mechanical thrombectomy may be options for a small subset of children with stroke and acute large vessel occlusion, improving acute stroke care for the majority of children likely rests in other areas.

Arteriopathy is the most common cause of arterial ischemic stroke in children. Genetic causes are myriad, and environmental associations include infection and trauma. McCrea et al[18] review genetic and environmental associations with pediatric cerebral arteriopathy with a focus on disease mechanisms. Although recent infection and trauma both predispose to arteriopathy, these risk factors are common, so an interaction between genetic predisposition and environmental factors seems necessary to lead to arteriopathy and stroke. Arteriopathy is known to increase the risk of recurrent stroke,[5] but clearly stroke subtype and pathophysiology matter for recurrence risk.

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Sickle cell disease represents the 1 area of pediatric stroke for which randomized controlled trials have been performed. These trials focused on primary prevention of strokes and secondary prevention of silent cerebral infarcts. Guilliams et al[19] review recent advances in causal pathways and physiological mechanisms of ischemic stroke in sickle cell disease, current therapy options, and include a summary of stroke prevention trials to date.

From this diverse set of articles on aspects of pediatric stroke care, we learn that research is needed in multiple areas. Children have decades to live with stroke-related deficits. Hence, stroke prevention, acute care, and rehabilitation are all important. Differences in stroke mechanisms and age at stroke onset impact response to therapies and recovery after stroke. Over the next decade, expect to see smaller, more homogenous groups of children studied carefully. The paradigm is the monogenetic disorder sickle cell anemia where pediatric clinical trials led to early transcranial Doppler ultrasound screening and therapies for primary stroke prevention that have reduced stroke risk by age 18 from 11% to 1.9%.[20]

Careful mechanistic, observational, and single-center pilot clinical trials are critically important. However, multicenter phase II and III clinical trials must be the next steps in pediatric stroke care to affect changes in clinical practice. A rare disease clinical trial approach is necessary,[21,22] because even with centers from across the globe, we will never achieve the sample sizes typically needed for proving treatment efficacy with a high-level of certainty in pediatric stroke. An additional challenge is that most rare disease trials occur in chronic illnesses, in which there is ample time to establish relationships with families for recruitment. In contrast, pediatric stroke presents acutely, and recruitment often must be rapidly completed. Given these challenges, a unified approach to investigating a few key questions at a time via clinical trials is critical. The most logical place to start is with high enrolling sites from existing large observational pediatric stroke studies[5,6] that have been built on the platform of the successful International Pediatric Stroke Study collaboration.[5,6,23] Avenues such as the National Institute of Neurological Disorders and Stroke clinical trials course for vetting study methods and training pediatric stroke investigators as well as partnerships with adult stroke clinical trialists are essential to build a strong pediatric stroke clinical trials network. Fortunately, a vibrant collaborative pediatric stroke research community exists that should be able to surmount these challenges.

Disclosures

None.

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