Symposium on Pediatric Stroke

Pediatric Stroke: Opportunities and Challenges in Planning Clinical Trials

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A conference entitled “Towards the establishment of clinical trials in pediatric and newborn stroke” assembled stroke animal model researchers, pediatric stroke researchers, adult stroke trialists, and members of the Food and Drug Administration and National Institute of Neurological Disorders and Stroke to focus on the obstacles and opportunities for conducting randomized trials in pediatric stroke. The need for good prospective clinical data in newborn and pediatric stroke in regard to outcome and recurrence risk was stressed. For clinical trials, there should be a scientific rationale. Preclinical data should be as promising and as complete as possible. Adult data should be explored, both positive and negative. For medication trials, reasonable safety and bioavailability data for the agent in question should be available. Commitment of researchers, collaboration with colleagues in primary care, emergency rooms, and intensive care units, and most importantly the willingness to participate of children and their families will all be crucial. Most children with cancer in the United States are enrolled in clinical trials and have an outcome superior to the adult patient with cancer, who is less likely to be enrolled in a trial. We should strive for enrollment and outcome results in pediatric stroke similar to those found in pediatric oncology trials.

Introduction

In December 2004 in New York, a three-day workshop was held entitled “Towards the establishment of clinical trials in pediatric and newborn stroke.” This conference assembled stroke animal model researchers, pediatric stroke researchers, adult stroke trialists, and members of the Food and Drug Administration and the National Institute of Neurological Disorders and Stroke to focus on the obstacles and opportunities for conducting randomized trials in pediatric stroke. Proceedings are published in papers in the current issue of Pediatric Neurology.

Although stroke is one of the ten most common causes of death in children, there has been no successful development or testing of effective preventions and treatments to date. We have reached a crucial point in pediatric stroke research. An increasing amount of research has been published in pediatric stroke during the past 10 years including cohort and case control studies. These studies are elucidating the epidemiology of stroke in infants and children, the risk factors, and outcomes to target for pediatric stroke treatment trials. The recent formation of a network of researchers focused on pediatric stroke has created a feasible mechanism for conducting clinical trials. Information gleaned from animal studies, pediatric clinical studies, and adult stroke studies was discussed in order to consider feasible next steps in treatment trial development.

The lack of research and evidence-based treatments in pediatric stroke are related to a number of challenges: nonstandardized approaches to diagnostic and outcome assessments, the common delay in recognition that a stroke has occurred in a child, and the failure of neuroprotective strategies that have worked in animal models to work in human trials, especially given the additional need in childhood stroke for animal models that reliably represent the physiology of the developing human brain. In addition, there are multiple and diverse etiologies and risk factors for stroke in children. Therapies proven in adult studies have not been tested in children for efficacy, and only scant data are available on safety. Finally, there are important maturational differences that limit the applica-
bility to children of research performed in adult stroke patients [1]. However, there are also a number of recent clinical and translational research studies that have increased our understanding of childhood stroke. Data on the epidemiology of stroke in children are available. The incidence of pediatric ischemic and hemorrhagic stroke is approximately 6/100,000 children per year [2]. Males are more likely to have a stroke, as are African-Americans. Stroke in African-Americans is more common even when excluding sickle cell anemia associated stroke. There is a 12% overall mortality, and 60% of those who recover have a permanent disability. The mortality numbers include newborn stroke, in which mortality is higher than in the older child. Evidence is conflicting regarding the relative incidence of hemorrhagic vs ischemic stroke. There are many etiologies for ischemic stroke in children, such as congenital heart disease, sickle cell anemia, moyamoya disease, Sturge-Weber syndrome, cavernous sinus angioma, and hereditary coagulopathies. No single risk factor predominates. Advances in laboratory testing, genetics, and neuroimaging have led to an understanding of a wider spectrum of stroke subtypes and risk factors.

Although there has been progress in understanding mechanisms of stroke in the immature brain, relatively more is known about perinatal than childhood stroke. Neuronal cell death induced by stroke or ischemia is influenced by age, and mechanisms of developmentally programmed cell death are easily triggered in the immature brain. Animal models of ischemic brain injury have largely been restricted to neonates, but there are some relevant data to be applied to childhood stroke. There is a model of middle cerebral artery occlusion in postnatal rats. Models such as fetal sheep, newborn lamb, and piglet have been used to study metabolic and physiologic end points. The development of stroke models in the immature animal involving temporary vascular occlusion provides a means to test treatments directed at the inflammatory cascade, apoptosis, and events that are associated with reperfusion injury.

There have been no prospective randomized treatment trials of stroke in children with the exception of those with sickle cell anemia. However, cohort studies have provided a resource for data regarding feasibility and safety of several antithrombotic agents in children [3]. These studies demonstrate important dosing effects, and that dose–response is age-related. These studies have been enhanced by the availability of sensitive diagnostic tests such as magnetic resonance imaging scans including diffusion-weighted imaging. Potential candidates for effective neuroprotection in children include hypothermia, inhibitors of free radical production, and free radical scavengers. The goal is to minimize neuronal damage by blocking autodestructive pathways and increasing the viability of penumbral areas.

The papers that summarize the conference in this issue of *Pediatric Neurology* highlight five areas: animal models, adult stroke trials, pediatric stroke knowledge, sickle cell stroke studies, and logistics of designing and implementing clinical trials.

The first paper by Dr. Vexler and colleagues summarizes the lessons from translational research in adult animal models of stroke. There are specific variables to consider in designing pediatric stroke animal models. There is compelling evidence that the brain’s response to either hypoxia-ischemia or stroke is age-dependent both in the degree and timing of apoptosis and in the inflammatory response. Several animal models are compared for suitability in studying aspects of pediatric stroke such as physiologic end points and long-term behavioral outcome. Strengths and limitations of a middle cerebral artery occlusion model are presented. There is consensus about using more and different animals before moving to clinical trials. Guidance on future directions includes using animal models to investigate the capacity of the developing brain for neuroplasticity and repair.

The paper by Pavlakis and colleagues discusses the lessons learned from the many failures and some successes of adult stroke trials. The conclusion: better animal models with dose–response curves, blinded outcome measures, and functional and histologic outcome measures will improve the preclinical studies. Phase 2 trials should examine safety, drug delivery, multiple end points, and surrogate markers as well as detect biological activity (Phase 2B). Phase 3 trials require recruitment strategies to be developed, stroke acute care delivery systems for children to be in place, better surrogate markers, and valid, reliable outcome measures.

Dr. deVeber and colleagues summarize the current data available in pediatric and newborn stroke. Most of the information available is descriptive but with the initiation of the International Pediatric Stroke Study (IPSS) funded by the Child Neurology Foundation, we now possess a database, a modification of the National Institutes of Health Stroke Scale for pediatric patients that is undergoing validity and reliability testing, and a valid and reliable outcome measure, the Pediatric Stroke Outcome Scale. Such validated pediatric stroke scales are necessary before any trials go forward. Widespread collaboration will be key, and an infrastructure and database featuring web-based data entry have already been created from which the first clinical trials in pediatric stroke can be planned and conducted.

Dr. Kirkham and colleagues summarize several major stroke prevention trials in children with sickle cell anemia that have been completed or are under way. The STOP I and II trials (Stroke Prevention Trial in Sickle Cell Anemia) are described, in which a high transcranial Doppler measured blood flow velocity predicted risk of stroke. A current trial to prevent further strokes in children with sickle cell anemia and silent strokes is described, as well as a pilot trial to use aspirin as a primary prophylaxis against stroke in children with sickle cell anemia.
Finally Dr. Hirtz and colleagues describe the organization and oversight necessary for multicenter clinical trials. Safety monitoring requirements are reviewed, and the role of the Food and Drug Administration is described. The rationale and appropriate use of the pilot trial vs the Phase 3 trial is discussed, and resources for guidelines in setting up clinical trials are included.

Our goal going forward is to emulate the pediatric oncologists. Most children with cancer in the United States are enrolled in clinical trials in contrast to adult oncology where only 3% of adults are enrolled in such trials [4]. Not surprisingly, the clinical outcome is much better in children compared with adults. We should strive for similar enrollment and outcome results in pediatric stroke.

There are a number of requirements for clinical trials in pediatric stroke to go forward. There should be a scientific rationale. Preclinical data should be as promising and as complete as possible. Adult data should be explored, both positive and negative. For medication trials, reasonable safety and bioavailability data for the agent in question should be available. Commitment of researchers, collaboration with colleagues in primary care, emergency rooms, and intensive care units, and most importantly the willingness to participate of children and their families will all be crucial to advancement of treatment of stroke in children. In 2005 we are well-positioned to bring these elements together in initiating stroke trials focused on the smallest of stroke victims, infants and children.

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References


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