Guest Editorial

Injury to the Preterm Brain and Cerebral Palsy

Bernard L. Maria, MD, MBA

Injury to the preterm brain and cerebral palsy was selected as the topic for the Eighth Neurobiology of Disease in Children Symposium, which was held November 5, 2008, in Santa Clara, California. Program Directors Drs Michael Johnston, Jan Brunstrom, and Enrik Hagberg prepared an outstanding agenda that included a panel of the most highly respected leaders in the field of preterm brain injury and cerebral palsy.

An estimated 60,000 children weighing <1500 g are born in the United States every year. While 90% of these patients survive, approximately 10% have the motor deficits of cerebral palsy and up to 50% have cognitive, behavioral, and social learning deficits. A complex interplay of destructive and developmental forces is responsible for injury to the preterm brain, and understanding basic mechanisms of encephalopathy of prematurity, hemodynamic thresholds (discussed by Dr Adre du Plessis), and periventricular leukomalacia (discussed by Dr Stephen Back)—including apoptotic mechanisms of cell death (discussed by Dr Henrik Hagberg), excessive glutamate release (discussed by Dr Frances Jensen), and infection/inflammation—are paramount to designing novel therapeutic interventions for the prevention and comprehensive management of cerebral palsy (discussed by Dr Jan Brunstrom). Interestingly, as discussed by Drs Joseph Volpe and Rebecca Folkner, in addition to white matter injury, neuronal and axonal injuries in the thalamocortical unit play important roles in the pathogenesis of cerebral palsy in the preterm infant. Dr Olaf Dammann is showing important connections between fetal inflammatory response and brain injury, and the presence of bacteria in the placenta significantly increases the risk of spastic diplegia in extremely low gestational age newborns. It is postulated that persistent brain inflammation may account for neurologic dysfunction for years.

Scientific advances in neuroimaging are showing diffuse, excessive high-signal intensity in the white matter (discussed by Dr David Edwards), and tract-based spatial methodologies are beginning to characterize axonal injuries and how they correlate with tissue microstructure, metabolic effects as seen with positron emission tomography imaging (discussed by Dr Diane Chugani), and clinical outcomes. In the rehabilitation field, there is increasing emphasis on prioritizing treatments that are supported by the highest level of evidence (discussed by Dr Diane Damiano), and research in activity-dependent cortical plasticity is showing that the effects of sensory loss impede motor learning.

The rapid pace of discovery in the basic neurosciences of injury to the preterm brain has not yet translated into effective new preventative therapies. What are the challenges for today’s child neurology practitioners? First, there is ongoing concern that high rates of prematurity contribute to a continuing high prevalence of very low birth weight neonates. Second, there is real concern that cascading molecular and biochemical disturbances in the brain are well established before the fetus at risk is clinically identified so that neuroprotective strategies will put many children at risk of drug toxicity and that drugs administered after birth are too late to abrogate significant nervous system damage. Although there is no real evidence in humans that antenatal therapy can alter the natural history of disease, an exciting National Institutes of Health (NIH)-funded pilot clinical study is underway (discussed by Dr Doe Jenkins), testing the glutathione precursor N-acetyl-cysteine that provides significant neuroprotection in animal models and is already US Food and Drug Administration (FDA)-approved for pregnant women. In addition stem cell therapies (discussed by Dr John MacDonald) hold promise for neuronal and enzyme replacement, growth factor repair, and neuroprotection.

After the daylong conference, a series of short podcasts of speakers and panelists were recorded and uploaded to the conference Web site (www.neurobiologyofdisease.com). These podcasts are an extremely valuable synopsis of the state of the field and outline where the focus should be in future research.

I wish to express my sincere appreciation to the National Institute of Neurological Disorders and Stroke,
the National Institutes of Health Office of Rare Disease, the Child Neurology Society, the Cerebral Palsy International Research Foundation, and the Kennedy Krieger Institute for co-sponsoring the conference and the Young Investigator Program that hosted 20 talented trainees and junior faculty with career interests in pediatric neurosciences and the field of injury to the preterm brain and cerebral palsy. I thank National Institute of Neurological Disorders and Stroke Director, Dr Story Landis, for her steadfast support of these conferences, and symposia directors, Drs Johnston, Brunstrom, and Hagberg, for ensuring quality presentations and discussions and for producing a wonderful symposium. I am truly proud of what Neurobiology of Disease in Children has contributed to the Child Neurology Society and I wish to express my deep gratitude to members of the Society for their strong support.

A specific aim of the Neurobiology of Disease in Children conferences is to disseminate symposia proceedings to ensure that clinicians and basic scientists are well informed about scientific advances, current research initiatives, and future directions. This issue of the Journal of Child Neurology features a series of papers prepared by conference participants and edited by Melanie Fridl Ross and myself. The first paper by Babcock and colleagues summarizes each of the sessions and includes the edited verbatim transcript of the conference’s question-and-answer sessions and panel discussions. Importantly, there are several original papers from the laboratories and programs of the speakers and panelists that are sure to be heavily downloaded and cited in the years ahead, including a paper by Dr Volpe on cerebellar vulnerability, by Dr Hagberg et al on mitochondrial roles in apoptosis, and one by Dr Singh’s group on the unexpected role of peroxisomes in childhood white matter disorders.

Muscular dystrophy has been selected as the topic for the Ninth Neurobiology of Disease in Children Symposium, which will be held October 14, 2009, in Louisville, Kentucky. Program Directors Drs Richard Moxley and Jeffrey Chamberlain have prepared an outstanding agenda that includes a panel of the most highly respected leaders in the field of muscular dystrophy. We look forward to seeing you in Louisville for another exciting symposium.

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