



Preface
Perinatal brain injury



Jeffrey M. Perlman, MB
Guest Editor

Despite great advances in our understanding of the mechanisms that contribute to injuries of the developing brain and the many attempts at prevention, perinatal cerebral injury remains a major cause of neonatal mortality and is associated with long-term neurodevelopmental sequelae. Potential mechanisms of injury are diverse and include hypoxia-ischemia, hemorrhage, perinatal infection or inflammation, metabolic disturbances, medications, and even the stressful intensive care environment. In a particular infant, a single event or a combination of factors may form the basis for injury, the extent of which may also be modulated by genetic influences.

In part based on these observations, this issue of the *Clinics in Perinatology* addresses some of the major clinical problems contributing to perinatal brain injury. The authors are outstanding clinicians from different specialties who through training, investigative research, and practice have developed expertise that either directly or indirectly relates to the development of brain injury. This allows for a unique opportunity to examine problems from different vantage points. For example, this issue includes a basic science discussion of the association of infection/inflammation and brain injury (first article), an infectious disease approach (second article), and a perinatologist's viewpoint (seventh article). Each author has responded superbly to the request to provide an overview of current concepts of pathogenesis and, where applicable, to provide the best available evidence for current therapeutic recommendations. Highlights from the contents of the twelve articles are briefly presented next.

In the first article, the biochemical cascades that contribute to the pathogenesis of neonatal hypoxic-ischemic brain injury are reviewed. In particular, the specific vulnerabilities that distinguish the response of the immature from the mature

brain are discussed, and the increased vulnerability of the developing oligodendrocyte is highlighted. The emerging importance of apoptosis as a mechanism of neuronal cell death is emphasized. In this regard, the recent experimental observations that minocycline, a drug that blocks caspase-3, a known effector of apoptosis, markedly protects the neonatal brain against hypoxic-ischemic brain injury is very exciting [1]. The second article deals with the very important association of chorioamnionitis and brain injury in the preterm and term infant. Some factors that may contribute to the unpredictable brain response to infection are highlighted, including developmental differences in susceptibility and differences in gene frequency as it relates to inflammation and thrombophilia. The third article deals with the important role of temperature in modulating the extent of hypoxic-ischemic brain injury. This is highly relevant given the recent observations that mild hypothermia improves neurological outcome following out-of-hospital cardiac arrest in adults [2,3]. Thus the results of two large multicenter studies (one already completed with long-term follow-up pending) using modest hypothermia as a neuroprotection strategy in infants at high risk for hypoxia-ischemia will be of critical importance to the clinician. Hypoglycemia remains a common clinical problem and is discussed in the fourth article. Although recurring pattern of injury in symptomatic hypoglycemia that involves parieto-occipital white matter as well as basal ganglia and thalamus is described (see also the 12th article), the mechanisms contributing to this increased specific predilection remain unclear and an important area for future research.

The fifth article, which reviews the postnatal management of the high-risk infant, includes two exciting clinical points of discussion: the role of oxygen versus room air in the delivery room resuscitation of the asphyxiated infant and the potential neuroprotective role of modest hypothermia (see also the third article). Focal cerebral infarction remains an enigma for the clinician and is discussed in the sixth article. Currently, there is an inability to predict which infants will develop this very important lesion. Thus, although we have long lists of causes and expansive and expensive tests, the diagnosis is initially suspected or diagnosed at the time of clinical presentation, usually late on the first or second postnatal day. The seventh article presents perinatal therapies that may modulate neurodevelopmental outcome, including the potential role of prophylactic antibiotics given to mothers with premature labor or prolonged premature rupture of the membranes. In the eighth article, the continued significant contribution of white matter injury—either in the presence or absence of hemorrhage—to subsequent major neurodevelopmental deficits, despite intervention strategies, remains a concerning problem.

The potential adverse neuronal effects of bilirubin and the potential impact on subsequent neurodevelopment are discussed in the ninth article. This subject is raised again in the 10th article, which examines numerous medical and neonatal environmental factors that may be important in the genesis of long-term cognitive and behavioral problems. This is rapidly becoming a major concern for clinicians, because up to 50% of very low birth weight graduates are exhibiting substantial cognitive and behavioral problems at long-term follow up. The therapeutic

approach to perinatally acquired infections is discussed in the 11th article. Of particular interest are current recommendations for neonatal herpes and cytomegaloviral infection with central nervous system involvement. In the 12th article, recent advances in neuroimaging are presented and the relevance to pathogenesis and treatment discussed.

This issue is clearly not all-inclusive, and important acute problems such as neonatal seizures are not specifically discussed. Our goal is that the information contained in this issue will facilitate patient care and serve as a stimulus for future research.

References

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- [2] Bernard, et al. *N Engl J Med* 2002;346:557–63.
- [3] Hypothermia Group. *N Engl J Med* 2002;346:549–56.

Jeffrey M. Perlman, MB
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, TX 75390-9063, USA
E-mail address: jeffrey.perlman@utsouthwestern.edu