Defining the True Pathogenesis and Pathophysiology of Neonatal Encephalopathy and Cerebral Palsy

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Over the last 25 years incremental knowledge has been gathered to better describe the role that acute hypoxic–ischemic injury may play in the origin of cerebral palsy. In 1986, Nelson and Ellenberg¹ observed that “despite earlier optimism that cerebral palsy was likely to disappear with the advent of improvements in obstetrical and neonatal care, there has apparently been no consistent decrease in its frequency in the past decade or two.” They concluded that the inclusion of information about the events of birth and the neonatal period accounted for a proportion of cerebral palsy only slightly higher than that accounted for when consideration was limited to characteristics identified before labor began. These observations were further strengthened 15 years later by sentinel publications by Badawi et al.^{2,3} in the Western Australian case–control study. An end point for these studies was moderate or severe newborn encephalopathy as opposed to cerebral palsy, realizing that many such cases of neonatal encephalopathy do not result in cerebral palsy.^{2,3} Similar to Nelson and Ellenberg¹ and Freeman,⁴ they observed that the causes of newborn encephalopathy are heterogeneous and many causal pathways start either preconceptionally or in the antepartum period. Looking specifically at the intrapartum period, they observed that there was *no* evidence of intrapartum hypoxia in over 70% of cases of newborn encephalopathy and that isolated pure intrapartum hypoxia accounted for only 4% of moderate-to-severe newborn encephalopathy. They further observed that intrapartum hypoxia may have been superimposed on preconceptional or antepartum risk factors with pre-existing insult in 25% of cases. Blair and Stanley⁵ reported substantially similar results; in only 8% of all the children with spastic cerebral palsy intrapartum asphyxia was the possible cause of their brain damage. In the final analysis, the incidence of neonatal encephalopathy attributed to intrapartum hypoxia, in the absence of any other preconceptional or

antepartum abnormalities, is estimated to be approximately 1.6 per 10,000 infants.^{2,3} It can also be stated with certainty that the pathway from an intrapartum hypoxic–ischemic injury to subsequent cerebral palsy must progress through neonatal encephalopathy^{2,3} and that hypoxic–ischemic encephalopathy is but a minor component of the broader diagnostic category of neonatal encephalopathy.

Criteria to define an acute intrapartum hypoxic event as sufficient to cause cerebral palsy, based on scientific evidence, were first proposed by the American College of Obstetricians and Gynecologists (ACOG).⁶ As knowledge was advanced by research, criteria were further refined by the International Cerebral Palsy Task Force Consensus Statement.⁷ Most recently, the criteria have again been reviewed and knowledge updated by the ACOG and American Academy of Pediatrics (AAP) Task Force on Neonatal Encephalopathy and Cerebral Palsy.⁸ The Task Force met over a 3 year period and utilized the services of expert consultants, concurrent literature review, as well as input and endorsement from many professional societies and organizations. The purpose of the Task Force was to define the current scientific evidence regarding the epidemiology, outcome, and etiology of neonatal encephalopathy. Review of the maternal risk factors, fetal considerations, antepartum events, and genetic conditions that could potentially serve as adverse events was undertaken. Also, a portion of the document is devoted to the assessment of the newborn infant including the relation of the following to neonatal outcome including cerebral palsy: umbilical artery pH, Apgar Score, role of neuroimaging and electroencephalography, placental pathology, nucleated red blood cells, and lymphocytic counts. Finally, a chapter on future directions summarizes possible therapies. The following organizations have reviewed and endorsed the document: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, the Child Neurology Society, the March of Dimes Birth Defects Foundation, the National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Society for Maternal Fetal Medicine, and the Society of Obstetricians and Gynaecologists of Canada. Accordingly, the latter publication is the most extensively peer-reviewed document of this subject published to date.

A description of the criteria required to define an acute intrapartum hypoxic event sufficient to cause cerebral palsy used in the Task Force Report is a modification of the International Cerebral Palsy Task Force Consensus Statement, *A template for defining a causal relation between acute intrapartum events*

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Editor's Note: Due to the important evolution of this area we are pleased to co-publish similar editorials by these authors in this issue and in Obstetrics and Gynecology.

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and cerebral palsy, published in the *British Medical Journal* in 1999.⁷ The use of these criteria will help to evaluate the probability that the pathology causing the cerebral palsy occurred during labor.⁸ The criteria reflect the current knowledge regarding the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy and are comprised of two parts. Four essential criteria make up the first part, and all four must be met: (1) evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7 and base deficit of ≥ 12 mmol/l), (2) early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation, (3) cerebral palsy of the spastic quadriplegic or dyskinetic type, and (4) exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders. Part 2 are criteria that collectively suggest intrapartum timing (within close proximity to labor and delivery, e.g., 0 to 48 hours), but are nonspecific for an asphyxial insult: (1) a sentinel (signal) hypoxic event occurring immediately before or during labor. A serious pathologic event has to occur for a neurologically intact fetus to sustain a neurologically damaging acute insult, (2) a sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent late or persistent variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal. The most frequently observed fetal heart rate patterns associated with cerebral palsy are those with multiple late decelerations and decreased beat-to-beat variability. However, these patterns cannot be used to predict cerebral palsy, as they have a false-positive rate of 99%.⁹ The high frequency (up to 79%) of nonreassuring patterns found during electronic monitoring of normal pregnancies with normal fetal outcomes makes both the decision on the optimal management of the labor and the prediction of current or future neurologic status very difficult,⁹ (3) Apgar scores of 0 to 3 beyond 5 minutes. There is good correlation between an extremely low Apgar score at 15 and 20 minutes and subsequent neurologic dysfunction,¹⁰ (4) onset of multisystem involvement within 72 hours of birth. Acute hypoxia sufficient to result in neonatal encephalopathy almost always involves multiple organs and not just the brain,^{11,12} (5) early imaging study showing evidence of acute nonfocal cerebral abnormality. Several patterns of brain injury may result from a hypoxic-ischemic episode in the fetus and are dependent on the severity of cerebral hypotension, the maturity of the brain at the time of injury, and the duration of the event.¹³

Hypoxic-ischemic encephalopathy is only a small subset of the broader category of neonatal encephalopathy and yet an even smaller contributor to the etiology of cerebral palsy. Failure to educate all concerned and vested parties has resulted in substantial capital and emotional cost. Only as our understanding of the

precise origins and pathophysiology of neonatal encephalopathy and cerebral palsy advances can logical hypothesis be designed and tested to reduce their occurrence. It is hoped that the publication of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy, "Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology" by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics report⁸ will go far to clarify the genesis of neonatal encephalopathy and cerebral palsy.

We encourage those engaged in research to pursue this very important area, and others to exert influence to the degree possible to propel this to a high priority for funding and study.

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