

We have invited select authorities to present background information on challenging clinical problems and practical information on diagnosis and treatment for use by practitioners.

Defining the Pathogenesis and Pathophysiology of Neonatal Encephalopathy and Cerebral Palsy

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The topics of neonatal encephalopathy and cerebral palsy, as well as hypoxic-ischemic encephalopathy, are of paramount importance to anyone who ventures to deliver infants. Criteria sufficient to define an acute intrapartum hypoxic event as sufficient to cause cerebral palsy have been advanced previously by both The American College of Obstetricians and Gynecologists (ACOG) and the International Cerebral Palsy Task Force. ACOG convened a task force that over the past 3 years reviewed these criteria based upon advances in scientific knowledge. In this review, we cover the slow but steady progression toward defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Four essential criteria are also advanced as prerequisites if one is to propose that an intrapartum hypoxic-ischemic insult has caused a moderate to severe neonatal encephalopathy that subsequently results in cerebral palsy. Importantly, all four criteria must be met: 1) evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH less than 7 and base deficit of 12 mmol/L or more), 2) early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks' 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. Other criteria that together suggest intrapartum timing are also discussed. (Obstet Gynecol 2003;102:628-36. © 2003 by The American College of Obstetricians and Gynecologists.)

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In 1862, the orthopedic surgeon Little advanced the hypothesis that the dominant causes of cerebral palsy were prematurity, asphyxia neonatorum, and birth trauma.¹ Little was partially correct inasmuch as a cesarean delivery exposed the mother to unacceptable risk to life or limb and medical decisions weighed heavily in favor of the mother as opposed to the fetus. Accordingly, vastly prolonged labors and difficult vaginal extractions, which have long since been abandoned, were at that time routine. Nevertheless, these proposed causes for cerebral palsy by far outlived these practices and in many circles remained unchallenged, whether by ignorance or convenience. However unintended, Little is the father of what has now become a global childbirth litigation industry.² Payments to children with cerebral palsy are some of the largest and in select states reach figures beyond \$40 million per case. Is it not egregious that legal fees often approach or exceed the actual dollar awards that the injured child receives? For obstetric health care providers, hospitals, and pregnant women we are at crisis stage, as liability insurance costs have forced many obstetric providers to withdraw these services in the United States.³⁻⁵ The crisis is also international: The British National Health Service currently is facing a medical negligence bill of \$4.2 billion.⁶

How then do we best proceed in the interest of both the women and children we strive to care for and our profession, which we hope to preserve? Although many potential roads may eventually lead to these destinations, the most direct would appear to be research and education. Additionally, these are our areas of strength and where the most immediate impact can be made. They are areas where each of us bears responsibility, especially with regard to the education of ourselves, our patients, the public, and the media.

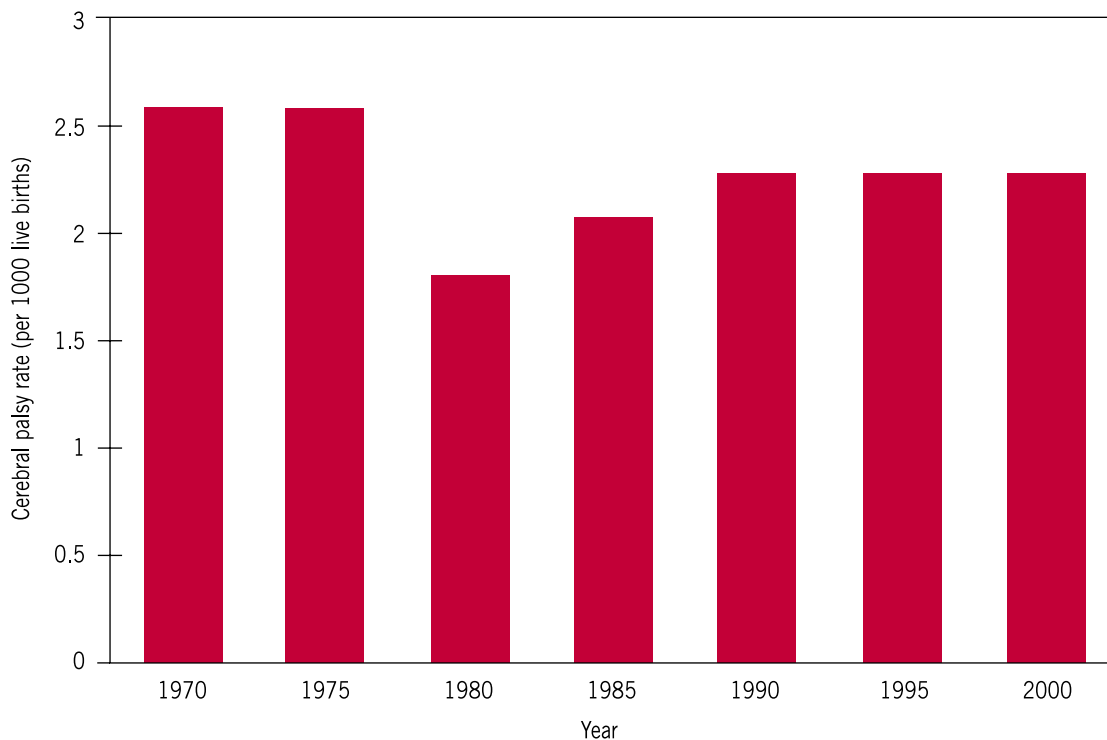


Figure 1. Cerebral palsy rates per 1000 live births, 1970–2000. Data from Clark and Hankins.⁸
Hankins. Neonatal Encephalopathy and Cerebral Palsy. Obstet Gynecol 2003.

The research journey, begun years ago, has progressed substantially over the last 25 years. In 1986, Nelson and Ellenberg⁷ 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” (Figure 1). 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 12 years later by sentinel publications by Badawi and colleagues^{9,10} 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.^{9,10} Similar to Nelson and Freeman,^{7,11} 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 encephalopa-

thy and that isolated pure intrapartum hypoxia accounted for only 4% of moderate to severe newborn encephalopathy (Figure 2). They further observed that intrapartum hypoxia may have been superimposed on preconceptional or antepartum risk factors with preexisting insult in 25% of cases. Blair and Stanley¹² reported substantially similar results; in only 8% of all of the children with spastic cerebral palsy was intrapartum asphyxia 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.^{9,10} 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^{9,10} 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, was first proposed by The American College of Obstetricians and Gynecologists (ACOG).¹³ As knowledge was advanced by research, criteria were further refined by the International Cerebral Palsy Task

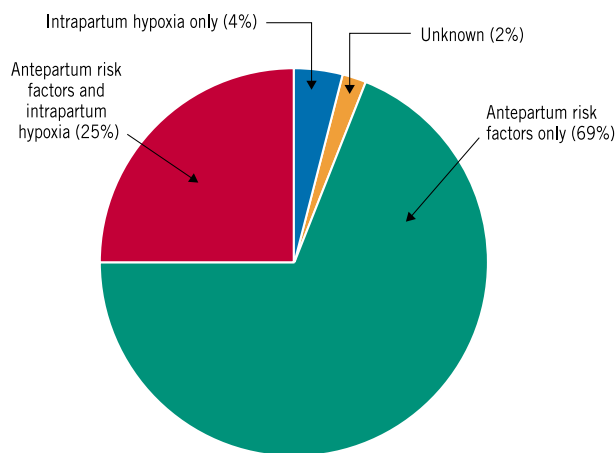


Figure 2. Distribution of risk factors for newborn encephalopathy. (Reprinted with permission from the BMJ Publishing Group. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, et al. Intrapartum risk factors for newborn encephalopathy: The Western Australian case-control study. *BMJ* 1998;317:1554–8.)

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Force Consensus Statement.¹⁴ Most recently the criteria have again been reviewed and knowledge updated by the ACOG and American Academy of Pediatrics Task Force on Neonatal Encephalopathy and Cerebral Palsy.¹⁵ Inherent in the review was liberal use of expert consultants and concurrent review, input, and endorsement from many professional societies and organizations including the Centers for Disease Control and Prevention, US Department of Health and Human Services, Child Neurology Society, March of Dimes Birth Defects Foundation, National Institute of Child Health and Human Development, National Institutes of Health, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 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 on this subject published to date.

A description of the criteria required to define an acute intrapartum hypoxic event sufficient to cause cerebral palsy follows. This is a modification and update of the International Cerebral Palsy Task Force Consensus Statement, “A Template for Defining a Causal Relation Between Acute Intrapartum Events and Cerebral Palsy,” published in *BMJ* in 1999.¹⁴ The use of these criteria will help to evaluate the probability that the pathology causing the cerebral palsy occurred during labor.

ESSENTIAL CRITERIA TO DEFINE AN ACUTE INTRAPARTUM EVENT SUFFICIENT TO CAUSE CEREBRAL PALSY (MUST MEET ALL FOUR)

1. *Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH less than 7 and base deficit of at least 12 mmol/L).* It has been demonstrated that a realistic pH threshold for significant pathologic fetal acidemia (ie, a pH associated with adverse neonatal sequelae) is less than 7.^{16–19} The metabolic component (ie, base deficit and bicarbonate) is the most important variable associated with subsequent neonatal morbidity in newborns with an umbilical artery pH of less than 7.²⁰ A base deficit of 12 mmol/L or greater is a reasonable cutoff criterion.²¹
2. *Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation.*^{14,22} Neonatal encephalopathy is a clinically defined syndrome of disturbed neurological function in the earliest days of life in the near term and term infant. If an intrapartum insult is severe enough to result in ischemic cerebral injury, abnormalities will be noted in the neurological examination within 24 hours after birth. The examination is characterized by abnormalities in 1) cortical function (lethargy, stupor, coma with or without seizures), 2) brainstem function (ie, pupillary and cranial nerve abnormalities), 3) tone (hypotonia), and 4) reflexes (absent, hyporeflexia).^{23,24} Outcome is related to the maximum grade of severity.²³ Thus, for infants with mild encephalopathy (stage I) outcome is invariably favorable, moderate encephalopathy (stage II) is associated with an abnormal outcome in approximately 20–25% of cases, and severe encephalopathy (stage III) is associated with a poor outcome in all cases.²⁴

Many cases of severe neonatal encephalopathy are not associated with intrapartum hypoxia, and the list grows continually.^{9,10,25,26} The associations with neonatal encephalopathy are diverse, with a representative listing in Figure 3.

3. *Cerebral palsy of the spastic quadriplegic or dyskinetic type.* Spastic quadriplegia and, less commonly, dyskinetic cerebral palsy are the only types of cerebral palsy associated with acute hypoxic intrapartum events.^{22,27} Although spastic quadriplegia is the most common subtype of cerebral palsy associated with acute hypoxic intrapartum events, it is not specific to intrapartum hypoxia.²⁷ Unilateral brain lesions are not the result of birth asphyxia; studies relating birth complications to neurological outcome indicate that hemiparetic cerebral palsy is not a result of known intrapartum asphyxial complications.^{28,29} Hemiple-

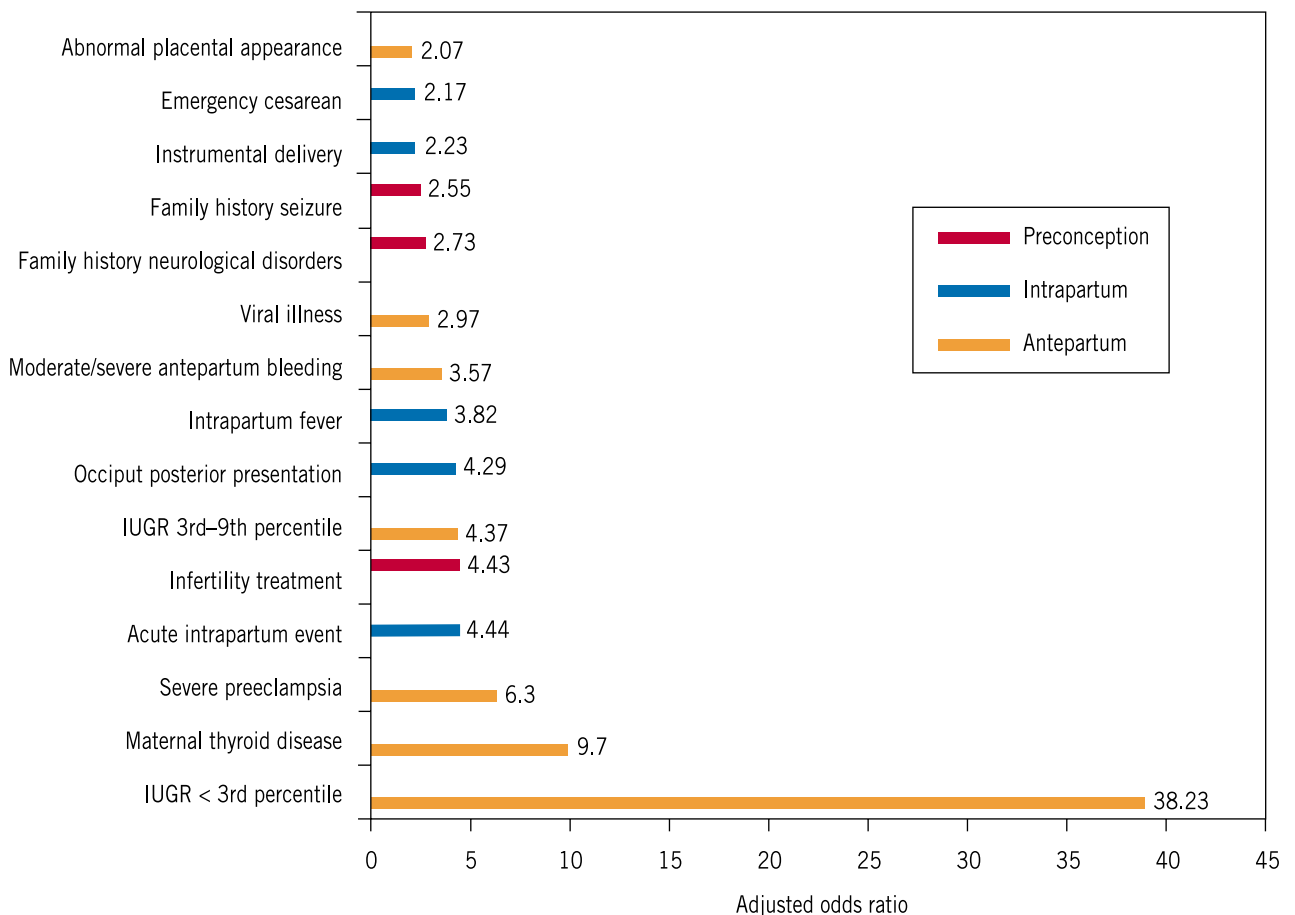


Figure 3. Risk factors for newborn encephalopathy. Data from Badawi et al.^{9,10}
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gic cerebral palsy, spastic diplegia, and ataxia have not been associated with acute intrapartum hypoxia.²⁹ Any progressive neurological disability is by definition not cerebral palsy and is not associated with acute hypoxic intrapartum events.

There is increasing information concerning another set of risk factors predisposing to fetal and neonatal strokes and thereby to hemiparetic cerebral palsy or, if bilateral, to spastic quadriparetic cerebral palsy.^{30–32} Such perinatal strokes commonly involve the middle cerebral artery, and many are related to inherited thrombophilias (of which the most common is the factor V Leiden mutation),³³ acquired disorders including antiphospholipid antibodies,³⁴ combinations of these, and environmental triggers.³⁵

Thromboembolic disease of the mother can be associated with obstetric complications and may be accompanied by placental thrombosis.³⁶ Embolization from the placenta into the fetal circulation is a probable intermediary event.³⁷

4. *Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders.* A large proportion of cerebral palsy cases are associated with maternal and antenatal factors, such as preterm birth, fetal growth restriction, intrauterine infection, maternal or fetal coagulation disorders, multiple pregnancy, antepartum hemorrhage, breech presentation, and chromosomal or congenital abnormalities.^{7,12,29,38,39} These causes must be considered and excluded before concluding that intrapartum hypoxia is the cause of cerebral palsy.

Inflammations and infections as well as thromboses and coagulopathies are recognized as being associated with white matter damage and cerebral palsy. Correlates of fetal infection include elevated fetal cytokine levels in both amniotic fluid and fetal blood. Research in animals and humans has shown an association between inflammatory markers and periventricular leukomalacia and neonatal encephalopathy.^{40–44}

Coagulation disorders such as antithrombin III deficiency, abnormalities of protein C or protein S, prothrombin genetic deficiencies, and the factor V Leiden mutation can lead to stroke.^{36,45-47} Also, occlusion of either arterial supply or venous return can cause permanent focal damage. Such damage may rarely be secondary to trauma in pregnancy, especially if in conjunction with an existing coagulation disorder. Early imaging studies may be very useful in identifying and evaluating a specific etiology.⁴⁸⁻⁵⁴

Numerous genetic and metabolic disorders can present clinically as neonatal encephalopathy; however, although there are many possible genetic causes, in most infants with neonatal encephalopathy the condition does not result from an identifiable genetic cause, and diagnosis in the perinatal period is unlikely unless there is heightened clinical suspicion based on specific findings or family history. The practitioner should attempt to identify such disorders by taking a family history, performing a thorough examination of the infant for dysmorphic features consistent with a genetic etiology, and ordering appropriate laboratory studies if warranted.

CRITERIA THAT COLLECTIVELY SUGGEST AN INTRAPARTUM TIMING (WITHIN CLOSE PROXIMITY TO LABOR AND DELIVERY—FOR EXAMPLE, 0–48 HOURS) BUT THAT 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. Examples of such sentinel events include a ruptured uterus, placental abruption, umbilical cord prolapse, amniotic fluid embolus, maternal cardiopulmonary arrest, and fetal exsanguination from either vasoprevia or massive fetomaternal hemorrhage.
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%.⁵⁵ 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 neurological status very difficult.⁵⁶

The Task Force endorsed the statement by the National Institute of Child Health and Human Development's Research Planning Workshop on electronic fetal heart rate monitoring,⁵⁷ which presented recommendations for standardized definitions of fetal heart rate tracings.

3. *Apgar scores of 0–3 beyond 5 minutes.* It is well established that the 1- or 5-minute Apgar score is a poor predictor of long-term neurological outcome in the individual patient.⁵⁸ For example, 75% of children with cerebral palsy have normal Apgar scores.⁵⁸

There is good correlation between an extremely low Apgar score at 15 and 20 minutes and subsequent neurological dysfunction. The enhanced correlation most likely reflects that those infants who are most injured and most depressed are resistant to resuscitation efforts. Additionally, in such cases where chest compressions, mechanical ventilation, and/or chemical resuscitation are either required or prolonged after birth, asphyxia may certainly superimpose additional injury. A score of less than 3 at 15 minutes was associated with a 53% mortality rate and a 36% cerebral palsy rate. When a low score persisted at 20 minutes, mortality was almost 60% and more than half (57%) of survivors had cerebral palsy.⁵⁸

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.^{59,60} Multisystem involvement may include acute bowel injury, renal failure, hepatic injury, cardiac damage, respiratory complications, and hematologic abnormalities.⁶⁰⁻⁶² Evidence of such injury should be sought in every case if an intrapartum cause is in the differential diagnosis.

With initial arterial hypoxemia, fetal cerebral vascular resistance can decrease by at least 50% to maintain cerebral blood flow with minimal impact on oxygen delivery.^{63,64} The clinical manifestations of the redistribution of cardiac output during severe asphyxia reflect the involvement of multiple organs (eg, necrotizing enterocolitis, persistent pulmonary hypertension, hypoglycemia, disseminated intravascular coagulopathy, release of nucleated red blood cells, oliguria or anuria, hyponatremia, fluid retention).^{59,62,65-70}

The timing of laboratory evaluations to help assess organ injury depends on the test desired. Samples for determination of brain- and myocardial-specific creatine phosphokinase levels should be obtained as soon as possible after delivery, as the half-life of these products is measured in hours. However, cardiac troponin I may be detected up to 4 days after myocardial injury.⁷¹ Serum aminotransferase levels increase within 12 hours of isch-

emic injury and peak approximately 24 hours after the acute injury.⁷² Elevated conjugated bilirubin levels occur later and may not resolve for several weeks after hepatic injury.⁷³ Acute elevations of serum ammonia are associated with severe hepatic injury.⁷⁴ Although an increase in urinary β_2 -microglobulin is a sensitive marker of proximal tubular injury, elevated levels may not be associated with clinical renal impairment.⁶⁶ Marked renal ischemia will result in acute tubular necrosis with oliguria and azotemia with progressive elevation of serum creatinine and blood urea nitrogen over several days after the acute ischemic insult.^{62,75} Elevated levels of plasma concentrations of arginine vasopressin after perinatal asphyxia also are found up to 48 hours after delivery.⁷⁶

Lymphocyte and nucleated red blood cell counts are elevated among neonates with fetal asphyxial injury. Both counts appear to be more elevated and to remain elevated longer in newborns with antepartum injury than in infants with intrapartum injury. However, the rapid normalization of lymphocyte counts in the neonate limits the clinical usefulness of these counts to the first several hours after birth.^{68,69}

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.⁵⁰

Early brain edema suggests recent insult. In the term infant, evaluation with magnetic resonance imaging and diffusion imaging shows reduced motion of water within hours of the injury.^{53,54} Between 24 hours and 7 days, other findings include elevated lactate levels and hyperintensity of gray matter. Later findings demonstrate cortical thinning and a decrease in the underlying white matter. In mild to moderate injury, the affected areas of the brain lie close to the inner table of the skull near the midline. In contrast, when the injury is more severe, the deeper brain substance is involved.⁷⁶ Magnetic resonance imaging is optimal for the evaluation of early injury.⁴⁸

CONCLUSION

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.⁷⁷ Only as our understanding of the precise origins and pathophysiology of neonatal encephalopathy and

cerebral palsy advances can logical hypotheses be designed and tested to reduce their occurrence. We encourage those engaged in research to pursue this very important area and others to exert influence to the degree possible to make this a high priority for funding and study. It is also apparent that our nation as a whole would be best served by allocating no-charge resources to allow these injured children to optimize their potential outcome. Could not the energy and resources invested in our current insurance and litigation system do greater societal good if redirected to scientific research for prevention and direct health care for those afflicted? The challenge belongs to all of us!

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