OBG MANAGEMENT

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Cerebral palsy: A look at etiology and new task force conclusions

An expert reviews new ACOG criteria on the link between hypoxic injury and cerebral palsy during childbirth and explores the unexpected role of technological advances.

Not only is cerebral palsy the most serious handicap of intrauterine and early neonatal life, it is the most common cause of medicolegal disputes in obstetrics.[1]

Using findings from a 2003 task force, this article outlines current understanding of the causes of cerebral palsy, summarizes the updated criteria for determining whether it is the result of an intrapartum event, and assesses the association between cerebral palsy and various factors, including prematurity and multiple gestation.

Prevalence

Cerebral palsy is the most common developmental disability in the United States; roughly half a million Americans have some degree of the disorder. In a surveillance program initiated by the Centers for Disease Control and Prevention (CDC), the average annual prevalence rate was 2.8 per 1,000 children (ages 3 to 10, 1991-1994).[2] Annually, at least 8,000 cases are diagnosed in infants, while almost 1,500 are identified in children of preschool age.[3]

KEY POINTS

- Cerebral palsy occurs as a result of an intrapartum event in no more than 10% of cases.
- Only cerebral palsy involving spastic quadriplegia is associated with an acute interruption of the blood supply, while purely dyskinetic or ataxic cerebral palsy generally is genetic in origin.
- Epidemiologic studies have clearly demonstrated a causal relationship between premature birth and cerebral palsy.

How hypoxemia leads to brain damage

Although the spectrum of current thought on cerebral palsy's etiology is beyond the scope of this article, the subject has been explored extensively in recent years.[4] We now know that no more than 10% of cases are the result of an intrapartum event.

Brain damage does appear to be the end result of a hypoxemic event. This event follows significant—usually abrupt—reduction in either the umbilical or uterine blood flow. Animal models demonstrate that even 12 hours of hypoxemia in midtrimester are sufficient to cause neuronal death.[5] During the third trimester, fetal hypoxemia of moderate severity—sometimes encountered in

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cases with placental insufficiency—also can cause brain damage. When hypoxemia occurs immediately before or during labor, it is called a "sentinel" event, usually involving such entities as premature placental separation, uterine rupture, acute maternal hypotension, prolapsed umbilical cord, ruptured vasa previa, and tightened true knot of the umbilical cord.

If the sentinel event is severe enough, the fetus dies in utero. Otherwise, a series of reactions occurs:

- Blood is redistributed to protect vital fetal organs such as the brain, heart, and adrenals. (This circulatory centralization is less feasible for preterm fetuses.)
- The hypoxia- and acidosis-induced vasodilatation in the brain is followed by hypoperfusion, a process that is facilitated by oxygen radicals.
- Finally, a reperfusion phase occurs, during which enzyme-mediated cellular damage is thought to result from a massive influx of calcium via damaged ion channels. At this phase, cellular injury is presumably caused by the inhibition of protein synthesis, the release of noxious agents, or by apoptosis. An intrauterine infection triggering the release of inflammatory agents may produce a similar effect.[4]

2003 task force redefines link between cerebral palsy and intrapartum event

It is seldom possible to determine the precise time brain damage occurs.[5] This issue often arises during medicolegal proceedings, when the parties try to ascertain any cause-and-effect relationship between intrapartum events and cerebral palsy.[6,7]

To address this question, in 1999 the International Cerebral Palsy Task Force—composed of obstetricians, neonatologists, child neurologists, and other clinical and scientific specialists—developed a set of criteria that defined when such a causal relationship existed.[5] These criteria were updated earlier this year by the American College of Obstetricians and Gynecologists (ACOG) Task Force on Neonatal Encephalopathy and Cerebral Palsy, in conjunction with the American Academy of Pediatrics.[8] The task force concluded that:

- while neonatal encephalopathy does not always lead to permanent neurologic impairment, "the pathway from an intrapartum hypoxic-ischemic injury to subsequent cerebral palsy must progress through neonatal encephalopathy";
- only cerebral palsy involving spastic quadriplegia is associated with an acute interruption of the blood supply;
- purely dyskinetic or ataxic cerebral palsy generally is genetic in origin; and
- most importantly, "approximately 70% of neonatal encephalopathy is secondary to events arising before the onset of labor."[8]

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Both task forces provide sound arguments that cerebral palsy has many causes, including developmental and metabolic abnormalities, infection, and autoimmune and coagulation disorders, as well as trauma and hypoxia in the fetus-neonate. In the updated criteria, 4 essential conditions must be met in order to define an acute intrapartum event as sufficient to cause cerebral palsy (**TABLE**). The task force also detailed nonspecific criteria that collectively may suggest an intrapartum timing of hypoxic injury.

These conclusions have been endorsed by a wide range of agencies and organizations, including the CDC, the US Department of Health and Human Services, the March of Dimes Birth Defects Foundation, and the National Institute of

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TABLE

Criteria that define an acute intrapartum hypoxic event as sufficient to cause cerebral palsy[8]

ESSENTIAL CRITERIA	COMMENTS
Metabolic acidosis (pH <7 and base deficit = 12 mmol/L)	• Samples taken from umbilical artery blood obtained at delivery • Cut-off levels based on risk to develop cerebral palsy • Neonatal acidemia may represent difficult resuscitation rather than asphyxia
Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation	• Usually develops within 24 hours of birth • Abnormal behavioral states are difficult to ascertain in preterm infants
Spastic quadriplegic or dyskinetic type of cerebral palsy	• Conditions like hemiplegia, spastic diplegia, ataxia, intellectual disability, autism, and learning disorder in a child without spasticity have not been associated with acute intrapartum hypoxia • Rett and Angelman syndromes should be excluded
Exclusion of other identifiable causes such as trauma, coagulation disorders, infectious conditions, or genetic disorders	
SUGGESTIVE BUT NONSPECIFIC CRITERIA	**COMMENTS**
A recognized sentinel event	• The fetus is tolerant of mild recurrent hypoxic events
A sudden and sustained fetal bradycardia or the absence of fetal heart-rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal	
Apgar scores of 0-3 beyond 5 minutes	• Low Apgar scores may represent effectiveness of resuscitation
Onset of multisystem involvement within 72 hours of birth	• Acute hypoxia does not affect just the brain
Early imaging study showing evidence of acute nonfocal cerebral abnormality	• After an acute insult, edema appears within 6-12 hours and clears by 4 days • Magnetic resonance imaging is the most informative modality

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Cerebral palsy through history: 2 opposing views

Although cerebral palsy has been around as long as humans have existed, it was not described in the medical literature until 1861, when Little outlined a sequence beginning with difficult labor, followed by neonatal seizures and, eventually, spastic motor paralysis.[1] (Interestingly, Little's disease—spastic diplegia—is not now believed to result from intrapartum events.)

The term "cerebral palsy" is usually attributed to Osler, who in 1889 associated the condition with asphyxia of the newborn following complicated deliveries.[2]

The first to question the cause-and-effect relationship between difficult birth and cerebral palsy was Sigmund Freud who, before turning to psychiatry, studied handicapped children. Freud noted that children with cerebral palsy often have other manifestations of brain damage that may have occurred during development in the early stages of gestation. Indeed, Freud surmised that brain damage might be an antecedent event to difficult birth.

The intrapartum asphyxia theory regained ascendancy in the late 1970s after experiments in primates demonstrated a causal link between perinatal asphyxia and brain damage. Since the same experiments could not be conducted in humans, the theory that cerebral palsy was caused by entities other than intrapartum hypoxia in roughly 90% of cases was based largely on epidemiologic evidence. (This theory maintained that even the 10% of cases with intrapartum signs compatible with damaging hypoxia may have had other antenatal causes.)

These 2 opposing views stimulated further investigations into the etiology of cerebral palsy.

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Child Health and Human Development. Of course, disagreement may arise about any of the criteria, especially if a case is subject to a lawsuit. Nevertheless, the conclusions of both task forces are quite logical. They also are likely to meet with widespread acceptance, since no serious objection or contrary view has yet been articulated, despite the fact that the first set of criteria has been in existence for several years.

Even so, it is important to remember that a much higher degree of certainty is necessary for scientific evidence ($P<.05$) than for evidence presented in a court case. It is therefore possible that courts may accept findings that are scientifically flawed.

The link to prematurity, birth weight, and fetal growth

Prematurity. Epidemiologic studies have clearly demonstrated a causal relationship between premature birth and cerebral palsy. Williams et al[9] found a cerebral palsy frequency of 3.2% among live births at less than 29 weeks' gestation, 2.8% at 29 to 32 weeks, and a remarkable decrease to 0.3% at 33 to 36 weeks' gestation and 0.07% at 37 or more weeks.

The major risk of premature birth is neonatal death. This is especially true for infants delivered in developing countries, where modern neonatal intensive care units (NICUs) are not available. Thus, it may be that premature infants of the Third World simply do not survive long enough to manifest signs of cerebral palsy.

On the other hand, in developed countries, where modern NICUs have undoubtedly improved the survival rates of premature neonates—even those at the edge of viability[10,11]—intact survival cannot be guaranteed. Because many premature births result

from potentially damaging maternal or fetal conditions, one could argue that prematurity-associated mortality lowers the incidence of cerebral palsy, which might otherwise affect survivors.

Birth weight. In recent long-term follow-ups of babies weighing less than 1,000 g at birth, researchers found that 24% to 25% of subjects had major neurologic abnormalities, 37% to 42% exhibited subnormal scores (less than 70) on the Bayley Mental Developmental Index, and 29% demonstrated subnormal scores (again, less than 70) on the Psychomotor Developmental Index.[12,13]

Fetal growth. Studies also appear to show a cause-and-effect relationship between chronic placental insufficiency leading to intrauterine growth restriction and cerebral palsy. In such cases, the already-affected fetus may exhibit intrapartum signs that prompt intervention, based on the assumption that the underlying cause of the fetal distress is still reversible.[5] This decision to intervene in the presence of presumable signs of fetal distress may later be erroneously considered evidence of an acute intrapartum event.

Increased rates in multiple births. Multiple pregnancy offers a useful example of how preterm birth, low birth weight, and aberrant fetal growth act in concert to increase cerebral palsy rates.[14]

Laplaza et al[15] compiled data from 11 cerebral palsy series and found a 7.4% average prevalence of twins among cerebral palsy cases. Studies from England and the United States have shown a similar prevalence of cerebral palsy in twins compared with singletons: 7.4 versus 1 in 1,000 survivors to 1 year[9] and 6.7 versus 1.1 in 1,000 survivors to 3 years.[16]

The prevalence of cerebral palsy in triplets exceeds that of twins and of singletons: 28 versus 7.3 versus 1.6 per 1,000 survivors to 1 year[17] and 44.8 versus 12.6 versus 2.3 per 1,000 survivors to age 3.[18] Japanese data confirm this trend in quadruplets, noting incidence rates of 11.1%, 3.1%, and 0.9% for quadruplets, triplets, and twins, respectively.[19] Taken together, the cerebral palsy prevalence among multiples exhibits an exponential relationship with plurality.[20]

Multiple and singleton pregnancies have similar risks for cerebral palsy until term. However, while the risk for singletons decreases with advanced gestational age and increased birth weight, the risk for multifetal pregnancies increases. The excess risk for cerebral palsy in twins beyond 37 weeks may be attributed to the likelihood that "term" occurs earlier in twins. In addition, multiple pregnancy offers unique "opportunities" for cerebral palsy, such as monochorionicity, twin-twin transfusion syndrome, single fetal demise, and anomalies.[14,20]

In the United States, an estimated 8% increase in the prevalence of cerebral palsy is due solely to the rise in multiple births.

Technology's unexpected role

It might be expected that modernized medical assessment and treatment would decrease the frequency of cerebral palsy. Two examples suggest the opposite.

Electronic fetal monitoring. Prompt cesarean section in cases of nonreassuring fetal heart-rate pattern does not decrease the rate of intrapartum brain damage. Nor has the implementation of electronic fetal monitoring during labor changed the incidence of cerebral palsy[21]—mainly because such monitoring has an extremely high false-positive rate.[5] In fact, except for the unequivocal normal pattern and the unmistakable pattern associated with potentially damaging acidemia (i.e., absent variability in the presence of persistent late or variable decelerations or bradycardia), the entire range of fetal

heart-rate patterns is subject to wide interpretation among clinicians as to appropriateness of intervention.[5]

Assisted reproductive technology. A significant proportion of multiple births result from assisted reproductive technology; these are rightly termed iatrogenic multiple pregnancies.[22] The estimated rates of cerebral palsy are significantly lower after spontaneous conception (2.7 per 1,000 neonates) than after the transfer of 3 embryos (16.86 per 1,000) or 2 embryos (8.77 per 1,000), or after the transfer of 3 embryos with a reduction of triplets to twins (10.31 per 1,000).[23] Kiely and colleagues[24] estimated that, in the United States, there is an 8% increase in the prevalence of cerebral palsy due solely to the rise in multiple births. This increase in multiple births is largely the result of infertility treatment.

Goals of research

At present, we are unable to identify the point at which brain damage becomes irreversible during pregnancy. Signs of fetal compromise, as in the case of suspected intrauterine growth restriction, are not sufficient to indicate earlier delivery, because it is unclear whether such a policy reduces the incidence of cerebral palsy without amplifying the risks of prematurely born infants.

One of the major difficulties in correlating events during pregnancy, labor, and early neonatal life with future outcome is that brain damage is usually diagnosed remotely from the event. We also lack qualitative and quantitative means of assessing the fetal brain at a cellular level.

Overcoming these obstacles would require the ability to obtain dysfunction signals at a subcellular level using noninvasive means. Use of various magnetic resonance imaging methods for brain assessment of neonates at risk for cerebral palsy is under investigation. The potential of such neuroimaging to differentiate reversible and irreversible antepartum brain damage appears promising. ■

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Dr. Blickstein reports no affiliations or financial arrangements with any of the manufacturers of products mentioned in this article.