REVIEW ARTICLE

MEDICAL PROGRESS

CEREBRAL PALSY
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MORE than 100,000 Americans under the age of 18 years are estimated to have some degree of neurologic disability attributed to cerebral palsy. Approximately 25 percent of the people with cerebral palsy identified by registries in France and the United Kingdom are unable to walk (even with help), and 30 percent are classified as mentally retarded. In the United States, the total annual cost to society of cerebral palsy has recently been estimated by the Advisory Council of the National Institute of Neurological Disorders and Stroke at $5 billion. Emotional suffering and lost opportunities add immeasurably to the burdens of affected families.

This past year was the 150th anniversary of Little’s attribution of cerebral palsy to difficult deliveries and the centennial of Freud’s suggestion that cerebral palsy might represent “symptoms of deeper-lying influences which have dominated the development of the fetus.” Yet the pathophysiologic mechanisms that underlie most of the cerebral palsy syndromes remain poorly understood. Recent reports suggest, however, that for the vast majority of children born at term in whom cerebral palsy later develops, the disorder cannot reasonably be ascribed to birth injury or hypoxic-ischemic insults during delivery.

The availability of neonatal intensive care units and high-technology diagnostic procedures has led to the survival of well-studied premature infants, in some of whom cerebral palsy later develops. Prematurely born children differ from children born at term in their higher incidence of cerebral palsy; the pathogenetic associations and clinical patterns of the disorder also differ between these groups. These differences and the relative contribution of obstetrical and neonatal care to the development of cerebral palsy are the focus of this review.

DEFINITIONS

Cerebral palsy is a symptom complex, rather than a specific disease. The most recent consensus definition states that cerebral palsy is an “umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development.” Postneonatal events such as meningitis, trauma, or occlusion of a cerebral artery or vein account for only 12 to 21 percent of all cases of cerebral palsy and are not the primary focus of this review.

In children, the relation between a lesion in the central nervous system and functional impairment may change over time. Abnormalities of motor tone or movement in the first several weeks or months after birth may gradually improve during the first year, and processes leading to the disappearance of cerebral palsy can continue after the first year. In the Collaborative Perinatal Project, approximately two thirds of the children with spastic diplegia and half of all children with cerebral palsy at their first birthday outgrew or lost the motor signs of cerebral palsy by the seventh year. Conversely, relatively nonspecific motor signs, such as hypotonia, that are seen in the first weeks or months of life may evolve over the first year or into spasticity and extrapyramidal abnormalities. The presumption is that myelination of axons and maturation of neurons in the basal ganglia are required before spasticity, dystonia, and athetosis can be manifested. Some have suggested that the definitive diagnosis of cerebral palsy be deferred until after the child’s second birthday. If the clinician suggests the diagnosis before the end of the child’s first year, then it should be presented to the family in tentative terms.

Cerebral palsy is classified according to the extremities involved (monoplegia, hemiplegia, diplegia, and quadriplegia) and the characteristics of the neurologic dysfunction (spastic, hypotonic, dystonic, athetotic, or a combination). The clinical manifestations often differ according to the gestational age at birth, the chronologic age, the distribution of the lesions, and the underlying disease.

Several other neurologic disabilities often accompany cerebral palsy. Approximately one third of all children with this disease have epilepsy; the prevalence among those with hemiplegia is 50 percent. A substantial number of those without cognitive impairment have visual–motor or other learning difficulties. The likelihood of epilepsy, extrapyramidal abnormalities, and severe cognitive impairment is higher among those with quadriplegia than among those with diplegia or hemiplegia. The high frequency of seizures and cognitive or perceptual disorders among patients who have cerebral palsy suggests that these disorders have common or related origins.

TRENDS IN INCIDENCE AND PREVALENCE

The prevalence of moderately severe or severe cerebral palsy is from 1.5 to 2.5 per 1000 live births. Estimates based on data from registers of children eligible...
for services, tend to be lower than those from prospective studies because, among other reasons, registers are likely to miss mild cases that can be diagnosed only by neurologic examination. During the past two decades, dramatic changes in obstetrical and perinatal care have included the increasing availability of fetal heart monitoring and fetal ultrasonography, the establishment of neonatal intensive care units, and the implementation of policies to encourage the regionalization of care and the transport of mothers carrying high-risk fetuses before delivery. If the occurrence of cerebral palsy reflected suboptimal obstetrical care, then its prevalence would be expected to decline in response to these remarkable improvements in care, but it has not done so. 

The rate of cerebral palsy per 1000 live births has increased in the lowest birth-weight groups in recent years, paralleling substantial increases in survival rates. The rate of cerebral palsy per 1000 surviving very-low-birth-weight infants has not increased, however, suggesting that cerebral palsy does not result from the hazards of intensive care, as has been suggested.

**Pathological Findings, Imaging Studies, and Clinical Patterns**

**Full-Term Infants**

Cerebral injury in the distribution of the middle cerebral artery is the most common finding in pathologically confirmed series of patients with hemiplegic, spastic cerebral palsy and in several series of patients with hemiplegia evaluated by computed tomography (CT) and magnetic resonance imaging (MRI). These assessments have demonstrated lost tissue (i.e., necrosis and atrophy) with or without gliosis, but it has not been possible to identify precisely when the ischemic or hemorrhagic disturbance was initiated. For reasons that are not yet clear, isolated right-sided hemiplegia occurs twice as frequently as isolated left-sided hemiplegia.

Some children with hemiplegic cerebral palsy have periventricular atrophy, suggesting the presence of abnormalities in the white matter, and about a sixth have gross malformations of cerebral development. The CT or MRI scan is normal in another one quarter to one third of children with presumed congenital hemiplegia. The lack of recognizable areas of injury or abnormality provides support for the notion that some cerebral palsy is related to abnormalities of brain development at the microscopic level and diminishes the likelihood that the disease is caused by injury to a normally developed brain. Indeed, in two separate studies, no abnormalities of any sort were identified in the obstetrical history of a majority of infants with hemiplegia.

In patients in whom cerebral palsy is manifested by quadriplegia, the motor impairment of the legs is equal to or more severe than that of the arms. Associated with this form of cerebral palsy are cavities that communicate with the lateral ventricles, multiple cystic lesions in the white matter, diffuse cortical atrophy, and hydrocephalus. Choreathetoid forms of cerebral palsy, which often include spasticity, tend to occur in infants who are born at term. Dystonia of the extremities also occurs frequently with spasticity but tends to be underrecognized. The microscopical appearance of the basal ganglia often resembles marble (status marmoratus). Persistently hypotonic, or atonic, cerebral palsy implies the involvement of cerebellar pathways. Long-tract signs such as brisk deep tendon reflexes and extensor plantar responses tend to accompany the hypotonia. An enlarged ventricular system is the most frequent correlate on neuroimaging.

**Infants Born Prematurely**

The prevalence of spastic diplegia or quadriplegia increased in Australia, Sweden, and the United Kingdom during the 1970s, along with an increase in the survival rate of infants born prematurely. This increase contrasts with the unchanged prevalence of quadriplegia among babies born at term during this interval.

During the past 30 years, neuropathologists have suggested that the periventricular white matter may be the site of the most important abnormalities leading to congenital motor dysfunction. Periventricular leukomalacia is the name given to the lesions characterized by foci of coagulative necrosis in the white matter near the lateral ventricles. The presence in the newborn brain of periventricular abnormalities believed to be forerunners of coagulative necrosis has prompted the broadening of the term "periventricular leukomalacia" to "periventricular leukomalacia complex" and "perinatal leukoencephalopathy."

In recent years, the term "periventricular leukomalacia" has come to be used, particularly with reference to findings on the ultrasound examination, to describe evidence of virtually any form of injury to white matter, including both hyperechoic (echodense) and hypoechoic (echolucent) areas. High-quality cranial ultrasonography through the open anterior fontanelle in premature babies has permitted clinicians to correlate later motor handicaps with particular patterns of cerebral abnormalities on ultrasound examination during the first postnatal weeks. Babies born before the 32nd week of gestation are at increased risk for both hyperechoic and hypoechoic lesions. By and large, the hyperechoic lesions represent vascular congestion or hemorrhage, and other early expressions of tissue injury, whereas the hypoechoic lesions appear to reflect the removal of necrotic tissue and the development of cyst-like structures, which tend to appear days or weeks later. Sometimes hyperechoic lesions diminish progressively without subsequently becoming hypoechoic.

Prominent hypoechoic periventricular areas on imaging studies predict the later development of motor dysfunction better than any clinical characteristic of the preterm newborn in the neonatal intensive care.
unit.63 Years later, people born prematurely in whom cerebral palsy develops have MRI scans characterized by prolonged T2 signals, especially in the periventricular areas (they are presumed to represent glial scars), distortion of the normal contours of the lateral ventricle (another finding presumed to be a consequence of glial scars), and ventriculomegaly (thought to reflect hydrocephalus ex vacuo caused by inadequate myelination of periventricular axons).55,69,70 Each of these MRI characteristics is probably a consequence of periventricular leukomalacia.

Premature infants who have ventriculomegaly without macrocephaly, even if they have never had documented hyperechoic or hypoechoic periventricular abnormalities, also appear to have an increased risk of cerebral palsy.71-89 Because preterm newborns who die with otherwise unexplained ventriculomegaly have early histologic evidence of periventricular leukomalacia (Fig. 2),90,91 it is possible that some babies with ventriculomegaly in whom cerebral palsy subsequently develops have diffuse periventricular leukomalacia below the detection level of even high-resolution ultrasonography. This hypothesis is supported by the recent finding that some children with cerebral palsy have repeatedly normal ultrasound scans during the weeks after birth but go on to have ventriculomegaly as well as other MRI abnormalities considered to be expressions of periventricular leukomalacia.88

**Risk Factors and Pathogenesis**

Some authors assume that problems during the birth process (such as midforceps delivery) and signs and symptoms in the newborn infant (such as low Apgar scores) are related to the subsequent development of cerebral palsy. However, their reports often fail to discuss the limitations of the studies on which these conclusions are based. Like most disorders, cerebral palsy has multiple risk factors, both causes and modifiers. For example, as Freud pointed out,92 difficulties during labor and delivery are most often seen among women who have had problems earlier in pregnancy.92 In an attempt to evaluate the relative contribution of all pregnancy-related factors, some epidemiologists have created analytic models that evaluate later events (for example, those occurring during the delivery) in the light of earlier events (characteristics of the mother before pregnancy, first-trimester events, and so on).10

In addition, strict definitions of terms are often lacking in studies of the pathogenesis of cerebral palsy. We strongly urge the use of descriptive definitions and the avoidance of the term "asphyxia" as synonymous with fetal distress, prolonged labor, difficult delivery, delivery with the umbilical cord wrapped around the neck, meconium staining, low Apgar scores, neonatal depression, intracranial hemorrhage, acidosis, or the absence of any other obvious cause for the newborn’s difficulties immediately after delivery.93 It is important to recognize that abnormal characteristics and exposures associated with cerebral palsy may be consequences of the processes leading to the disease and not its cause.94,95 These include twin gestation, an unusually short or long interval between the pregnancy with the child affected by cerebral palsy and an earlier pregnancy, a history of spontaneous abortion and stillbirth, the need for thyroid hormones or estrogen during pregnancy, malpresentation, postmaturity, low Apgar scores, abnormal fetal heart rate during labor, and congenital anomalies. More than 95 percent of infants with any one of these risk factors do
not have cerebral palsy. Recurrent neonatal seizures, which predict later cerebral palsy better than other perinatal characteristics, may be a consequence, rather than a cause, of the processes that lead to cerebral palsy. Support for the view that newborn seizures are not a cause of cerebral palsy comes from the observation that among infants with newborn seizures, those whose seizures last the longest are not at higher risk of later impairment than those whose seizures are brief.

Finally, some studies of cerebral palsy, including most of those that evaluate cerebral images of children and adults with cerebral palsy, are based on relatively small numbers of subjects and do not take into account the issue of selection bias. For example, in these days of cost containment, physicians are more likely to order an MRI scan of the brain of a child with cerebral palsy if that child has evidence of a worrisome neurologic change. Thus, MRI scans of such children and adults should not be viewed as representative of all patients who have cerebral palsy.

Full-Term Infants

Recently published prospective studies do support a number of earlier reports that cerebral palsy is associated with certain prenatal risk factors (Table 1). We classify risk factors for cerebral palsy into three groups according to whether they occur before pregnancy, during pregnancy, or during the perinatal period.

Factors Occurring before Pregnancy

A child whose mother has long intervals between menses appears to be at increased risk for cerebral palsy. The risk is increased if there has been an unusually short interval (less than three months) or an unusually long interval (more than three years) since the previous pregnancy. In addition, mothers of children with cerebral palsy are more likely than other mothers to have a history of spontaneous abortion and stillbirth. These findings indicate that maternal menstrual and obstetrical factors convey information about the risk of cerebral palsy.

The association of a family history of early-onset, nonprogressive motor impairment with cerebral palsy, especially when the impairment is linked with specific chromosomal, metabolic, or morphologic aberrations, is in keeping with a genetic basis for some cases of the disease. The greater concordance for cerebral palsy among monozygotic than among dizygotic twins also suggests a genetic basis, but it is compatible with placental problems that are unique to monozygotic twins as well.

Factors Occurring during Pregnancy

Two of the leading predictors of cerebral palsy in the Collaborative Perinatal Project were congenital malformations and birth weight below 2001 g. Children destined to have cerebral palsy are more likely than other children to have both major and minor physical malformations that undoubtedly reflect perturbations in normal prenatal development. Newborns who subsequently have cerebral palsy tend to have a lower body weight and a smaller head circumference than their unaffected peers. This is true for preterm newborns who subsequently have spastic diplegia, as well as for babies born at term who eventually have other forms of cerebral palsy.

Twins are more likely than singletons to have antenatal periventricular leukomalacia and cerebral palsy. Some of the increased risk of cerebral palsy among twins probably results from their gestational age and intrauterine growth retardation. In one study, an increase in the cesarean-section rate in the delivery of twins was not associated with a reduction in the prevalence of cerebral palsy.

Mothers known to have been hyperthyroid or who were prescribed thyroid hormones or estrogen in pregnancy have been found to be at increased risk of giving birth to a child in whom cerebral palsy later develops. This association is especially intriguing in the

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<th>Table 1. Factors Identified in Epidemiologic Studies as Associated with Cerebral Palsy.</th>
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<td>Before pregnancy</td>
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<tr>
<td>History of fetal wastage</td>
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<td>Long menstrual cycles</td>
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<td>During pregnancy</td>
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<td>Low social class</td>
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<td>Congenital malformation</td>
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<td>Abnormal fetal presentation</td>
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<td>During labor and delivery</td>
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<td>Premature separation of the placenta</td>
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<td>During the early postnatal period</td>
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<td>Newborn encephalopathy</td>
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light of an epidemic of spastic diplegia, mental retardation, and deaf–mutism in the New Guinea highlands that was attributed to iodine deficiency.  

Factors Occurring during the Perinatal Period

Among children born before the modern era of neonatal intensive care, those delivered by mothers whose placentas showed evidence of chorioitis were more likely than others to have cerebral palsy.  

Because chorioitis is associated with prematurity, the link may be stronger now because of both the increased survival of those with the highest risk of cerebral palsy and the association between periventricular leukomalacia and amnionitis (a complication of chorioitis).  

Chorioitis may contribute to cerebral palsy either directly or indirectly by increasing the risk of prematurity.

Non-vertex and face presentations of the fetus are associated with an increased risk of cerebral palsy.  

One interpretation of this fact is that an abnormal presentation does not cause cerebral palsy, but rather may be a marker of preexisting difficulties. According to this hypothesis, fetuses with hypotonia and other abnormalities that will later be manifested as cerebral palsy are less able than others to move into a vertex position.

A body of literature attests to the weak association between intrapartum asphyxia and the subsequent development of cerebral palsy. Often evaluated are nonspecific surrogates, such as fetal bradycardia (identified by auscultation or cardiotocography), passage of meconium during labor, low Apgar scores, and newborn encephalopathy. Acidosis, which might be viewed as a more specific indicator of asphyxia, also fails to contribute much predictive information about the risk of later motor handicap.

Infants Born Prematurely

The rate of later cerebral palsy is 25 to 31 times higher among infants who weigh less than 1500 g at birth than among full-sized newborns. Babies whose birth weight is less than 2500 g account for about one third of all babies who later have signs of cerebral palsy.

In the past, the focus of attention in ultrasound examinations of premature infants was the ventricular system and the periventricular areas, because of the presumed importance of hemorrhage adjacent to or in the ventricles. Now the emphasis is on the white matter, because periventricular leukomalacia predicts cerebral palsy much better than do intracranial hemorrhages.

Between 22 percent and 100 percent of premature infants who have ultrasonographic findings considered to be characteristic of periventricular leukomalacia later have cerebral palsy. The rates tend to be higher for images showing hyperechoic areas than for those showing hyperechoic areas, and highest for large, posterior, and bilateral lesions. Selection of the infants with more obvious and severe abnormalities for ultrasound study may have biased the results toward the high percentages reported.

Clues to the epidemiologic features of cerebral palsy among infants born prematurely can be obtained from an examination of the epidemiologic features of periventricular leukomalacia as defined by ultrasonography (Table 2). As a generalization, the lower the birth weight and the gestational age, the higher the risk of cerebral palsy and periventricular leukomalacia.

Thus, it should not be surprising that a number of correlates of low birth weight and early gestational age are associated with periventricular leukomalacia, even among babies born prematurely. These include low Apgar score, acidosis, hypopapnia, pneumothorax, recurrent apnea, patent ductus arteriosus, hypotension, and the need for transfusion. Separating the contribution of prematurity to periventricular leukomalacia (or cerebral palsy) from the contribution of the correlates and consequences of prematurity poses problems of inference that have yet to be resolved.

Periventricular leukomalacia is often referred to as a hypoxic–ischemic lesion. The main epidemiologic evidence for this idea is that babies with periventricular leukomalacia tend to have lower blood pressure than their peers. However, this finding has not always been reproducible.

Babies with paraventricular hyperechoic areas on imaging studies are consistently more likely than other babies to have intracranial hemorrhage. One hypothesis offered to explain this association is that the hemorrhage impedes venous return, resulting in venous infarction and subsequent white-matter injury. Alternatively, intracranial hemorrhage and periventricular leukomalacia may share common risk factors.

Other ideas about the cause of periventricular leukomalacia emphasize neurochemically mediated injury to white matter. One hypothesis is that infections
that prompt delivery at the beginning of the third trimester result in the release of cytokines (such as tumor necrosis factor alpha) that damage developing white matter.\textsuperscript{114} According to another theory, based on recent in vitro studies and studies in animals, free radicals and released neurotransmitters (such as glutamate) promote necrosis.\textsuperscript{116}

**PREVENTION**

Although only 9 percent of patients with cerebral palsy in the Collaborative Perinatal Project lacked a major congenital malformation or other intrinsic defect (birth weight under 2001 g, microcephaly, and so on), Nelson and Ellenberg\textsuperscript{10} wrote in the *Journal of Pediatrics* in 1986, "Of the . . . mother-infant pairs in the 5 percent with the highest risk [for cerebral palsy], only 2.8 percent produced a child with cerebral palsy; the false positive rate was thus 97 percent." Epidemiologic studies published since then have not provided any reasons to change the impression that our ability to identify modifiable, presumed causes of cerebral palsy is limited.

In preterm newborns, periventricular leukomalacia has been associated with physiologic instability in the form of low blood pressure, ventilatory problems, and infection.\textsuperscript{53} Thus, it would appear that further improvements in neonatal care may reduce the risk of periventricular leukomalacia and consequently of cerebral palsy in preterm infants. Full-term babies with newborn encephalopathy have a greatly increased risk of later neurologic handicaps, including cerebral palsy.\textsuperscript{12,115} An overabundance of excitatory amino acids has been offered as an explanation for newborn encephalopathy.\textsuperscript{131,140} Extrapolating from this concept has led to the hypothesis that an overabundance of excitatory amino acids during the first postnatal days also contributes to permanent neurologic damage.\textsuperscript{140} However, the administration of drugs designed to interfere with excitatory amino acids, such as N-methyl-D-aspartate-receptor antagonists, entails risks,\textsuperscript{141} and criteria for their administration have yet to be determined.

**CONCLUSION**

The burden imposed by cerebral palsy on society has not abated despite recent advances in medical care. Indeed, the increased survival of preterm newborns at risk for the disease has resulted in an increased number of children with cerebral palsy, mainly of the spastic diplegic variety. Efforts to prevent periventricular leukomalacia are most likely to reduce the occurrence of cerebral palsy among those children born in the third trimester. Cerebral palsy in children born at term most often appears to reflect phenomena that precede the onset of labor. Thus, efforts to prevent cerebral palsy will require a focus on factors and events during pregnancy, including those that predispose the mother and fetus to preterm delivery.

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