REVIEW ARTICLE

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Prenatal Factors in Singletons with Cerebral Palsy Born at or near Term

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Cerebral palsy, a congenital motor disability of cerebral origin, is a group of lifelong movement disorders affecting about 2 of every 1000 children. Although defined as a motor disorder, cerebral palsy is often accompanied by intellectual deficits, epilepsy, and sensory disabilities. Cerebral palsy is expensive in human and economic terms. No cure is available, so effective strategies for primary prevention are highly desirable, but their development requires an understanding of causal pathways.

Gestational age at birth is strongly associated with cerebral palsy, with a prevalence among term infants that is about one fortieth the prevalence among extremely preterm survivors.[1] Research has focused on very preterm infants, as warranted by the high individual risk faced by such infants, but less than 0.4% of neonatal survivors are born before 28 weeks of gestation.[1] The 96% of singletons born at or after 35 weeks of gestation, who account for two thirds of newborns with cerebral palsy,[1] have been less extensively studied, and for them, much of the medical and lay literature on the causes of cerebral palsy remains focused on the contribution of birth asphyxia.

Continuous electronic fetal monitoring during labor was introduced to identify fetal asphyxia, with the expectation that timely intervention would prevent cerebral palsy. Unfortunately, that expectation has met with disappointment. Despite there being a marked increase in surgical deliveries associated with fetal monitoring, as well as accompanying increases in risks and costs, there has been no decrease in the numbers of live births with cerebral palsy over the past three decades (Fig. 1).[2,3]

Controlled studies in human populations have shown important prenatal antecedents of cerebral palsy.[4-13] A 2004 report concluded, "Evidence suggests that 70 to 80% of CP [cerebral palsy] cases are due to prenatal factors and that birth asphyxia plays a relatively minor role (<10%)."[9]

The development of large population-based data sets that include information from cerebral palsy and birth defects registries permits further clarification. In one large, prospective, population-based study, 91.5% of term and near-term singletons with cerebral palsy had had no recognized potentially asphyxiating birth event; however, fetal growth restriction and major birth defects occurred substantially more frequently in infants with cerebral palsy than in controls matched for gestational age.[11] Studies of placental disorders[14] and genetic investigations[15,16] have provided evidence that prenatal processes are important not only for cerebral palsy but also for neonatal encephalopathy, which precedes cerebral palsy in about 20% of cases in term and preterm children.[11]

Studies documenting the importance of prenatal factors in term infants with cerebral palsy have had limited influence on clinical and experimental perinatal medicine. In this review, we discuss the evidence that for children in developed countries who are born at or near term, factors operating before labor begins are chief determinants of the risk of cerebral palsy.

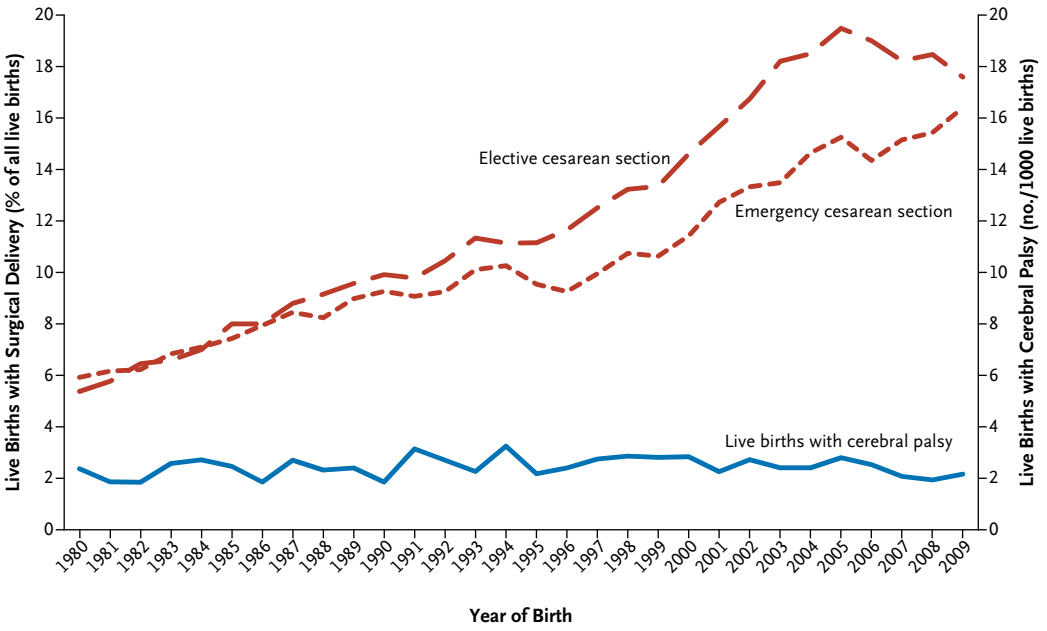

Figure 1. Elective and Emergency Cesarean Sections and Live Births with Cerebral Palsy in Western Australia, 1980–2009.

Shown are the proportions of live births with delivery by elective cesarean section before the onset of labor or membrane rupture and without induction, live births with delivery by emergency cesarean section (with the timing determined by an arising complication), and all live births with cerebral palsy. The increasing proportions of both elective and emergency cesarean deliveries since 1980 have not been accompanied by any change in the proportion of live births with cerebral palsy.

DEFINITIONS

Cerebral palsy is a disorder of movement affecting activities of daily living that is due to nonprogressive cerebral defects acquired early in life. Many perinatal clinical trials and studies of the causes of cerebral palsy have excluded infants with recognized neural-tube and other birth defects. If birth defects are excluded, their role in cerebral palsy cannot be investigated and may be overlooked.

We use the term "birth defects" inclusively to indicate structural or functional defects present at birth, including malformations, deformations, and antenatal injury, regardless of cause, since the cause is frequently unclear. The defect must be present at birth, so microcephaly and hydrocephaly developing in infancy or early childhood are not considered, although they may be the result of defects that were present at birth.

There is no general consensus about what constitutes a major defect as compared with a minor defect. We use the term "birth defects" except when citing authors who use "congenital malformations" or other terms or when referring specifically to malformations. The evidence discussed here comes, when possible, from population-based studies of infants.

BIRTH DEFECTS AND CEREBRAL PALSY

The earliest controlled studies and subsequent investigations of the cause of cerebral palsy have shown that birth defects are observed more frequently in persons with cerebral palsy than in those without the disorder. Eastman and DeLeon reported in 1955, an era when few very preterm infants survived, that congenital malformations were more frequent in persons with cerebral palsy than in controls.[4] A later study[17] confirmed the excess of congenital malformations in cerebral palsy and noted "a large number of cases in which either microcephaly or hydrocephaly was encountered" but did not distinguish head-size abnormalities that were present at birth from

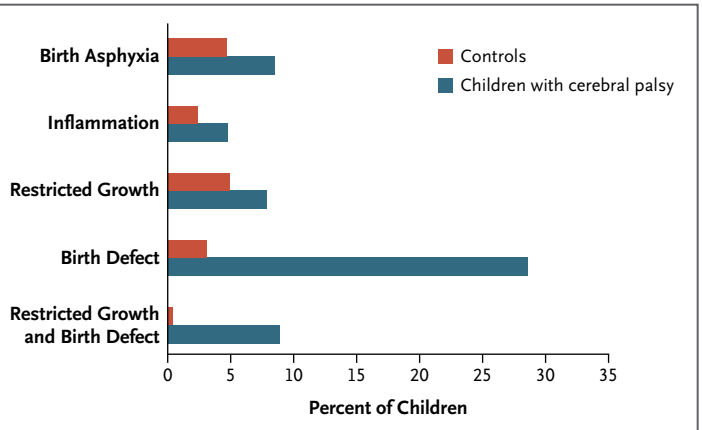

Figure 2. Distribution of Four Major Risk Factors in Singleton Children with Cerebral Palsy Born at a Gestational Age of at Least 35 Weeks, 1980–1995.

Data are from a study of 496 children with cerebral palsy and 508 controls. The four risk factors were a potentially asphyxiating intrapartum event, evidence of inflammation, fetal growth restriction (defined as a birth weight that was more than 2 SD below the optimal weight for gestation, sex, maternal height, and parity, or a neonatal diagnosis of fetal growth restriction), and a major birth defect. Data shown are for one or more of these risk factors in at least 2% of children with cerebral palsy or controls. Major birth defects were the most frequently occurring risk factor in children with cerebral palsy, and when combined with fetal growth restriction, they were associated with the highest relative risk.

those that developed postnatally. In a study by Malamud et al.,[18] autopsies of 68 institutionalized persons with cerebral palsy showed cerebral malformations in 35% and cerebral destructive processes in a similar proportion. These early studies established that birth defects occur in excess in persons with cerebral palsy but did not consider the representativeness of the study samples or the possibility that gestational age or the timing and methods of identifying birth defects might influence the findings.

In the Collaborative Perinatal Project, three times as many major malformations outside the central nervous system were identified by 1 year of age in children with cerebral palsy as in children without cerebral palsy.[5] Other investigations have confirmed the association of birth defects with cerebral palsy, as examined within gestational age or birth weight strata.[19-24]

In an investigation linking a cerebral palsy registry with a state registry of birth defects recognized by the age of 6 years, the contribution of birth defects to cerebral palsy in singletons with a gestational age at birth of at least 35 weeks markedly exceeded the contribution of other major factors, including potential birth asphyxia (Fig. 2).[11] Factors not examined in that study are also known to play a role in cerebral palsy, including coagulopathies and several maternal disorders,[25-28] but none are known to be a major contributor. Another study showed that the combination of birth defects and fetal growth restriction was associated with a marked increase in the risk of cerebral palsy.[29]

A number of neurodevelopmental disorders may have mechanisms in common.[30-32] One study showed that more than a third of infants with neonatal seizures had a major malformation, as did half of those with tonic or myoclonic epilepsies in childhood.[33] Of infants with neonatal encephalopathy in a population-based study, 27.5% had a birth defect, as compared with 4.3% of controls.[34]

Birth defects can escape detection in the newborn period,[35] so their ascertainment is more likely to be complete with longer periods of observation. With increased use of imaging studies in sick newborns, early detection of birth defects has improved, but asymptomatic neonates may not be fully evaluated. Imaging procedures add greatly to the identification and description of anomalies but were not available in the past and are not systematically included in many population-level studies. In addition, tools for imaging differ in sensitivity; for example, magnetic resonance imaging is more sensitive than ultrasonography or computed tomography for detecting cerebral malformations.

GESTATIONAL AGE

Low gestational age at birth is strongly related to an increased risk of cerebral palsy. Therefore, any inquiry about the role of birth defects in cerebral palsy must consider whether the risk is increased through an association with early birth.

In the general population, birth defects are more often detected in preterm infants than in term infants, and substantially more often in very preterm infants.[36] In striking contrast, among infants with cerebral palsy, major malformations are more frequent in infants born at term or at normal birth weight.[19,37] The risk of an association of birth defects with cerebral palsy is increased by a factor of 9 among infants born at or near term as compared with preterm infants.[19] The high prevalence of birth defects among children with cerebral palsy born at term has been confirmed repeatedly[20-24] and is most marked for brain and cardiac anomalies.

An explanation for the high prevalence of

birth defects among children with a low gestational age at birth in the general population might be that adverse conditions leading to malformation also contribute to delivery before term. It is not obvious what accounts for the opposite pattern in cerebral palsy (i.e., a high rate of anomalies at the normal time of delivery).

CEREBRAL DEFECTS

Not surprisingly, the birth defects most frequently associated with cerebral palsy in term and near-term infants involve the brain. Congenital cardiac lesions are the next most common defects in such infants, although major defects in most organ systems are overrepresented (Fig. 3). Birth defects of the brain include structural abnormalities, aberrant growth, and prenatal destructive lesions. Cerebral defects may be identified by gross inspection, by measurement of head size, or by neuroimaging. Congenital microcephaly or macrocephaly — in which head circumference is substantially smaller or larger, respectively, than that in a reference population — is overrepresented in cerebral palsy. In neonates in general, variations in skull and soft-tissue thickness are not marked, and head size is a good indicator of brain size.

Congenital hydrocephaly (increased ventricular size) can be reliably identified, and its anatomical basis defined, only by means of cranial imaging. Some studies have inferred the presence of congenital hydrocephaly on the basis of excessive head size rather than imaging findings, risking confusion with benign macrocephaly, whereas other studies have documented only the underlying anatomical cause of a large head as a birth defect, but not head size itself. In addition to the adverse effects of disorders leading to macrocephaly, a large head itself may cause mechanical problems during delivery.[38]

Congenital microcephaly is the most common birth defect in cerebral palsy. The differential diagnosis for congenital microcephaly is extensive: von der Hagen et al.[39] list 19 monogenetic forms of microcephaly, at least 4 trisomies, an imprinting disorder, metabolic disorders of genetic cause, and a range of infections, teratogens, and disruptive events such as prenatal stroke. The Developmental Brain Disorder Database lists 142 genes associated with congenital microcephaly and 17 syndromes.[40] Some antecedents of congenital microcephaly cause isolated smallness of the brain, whereas others lead to smallness of both brain and body. Only approximately half the cases of microcephaly have a recognizable cause.[39]

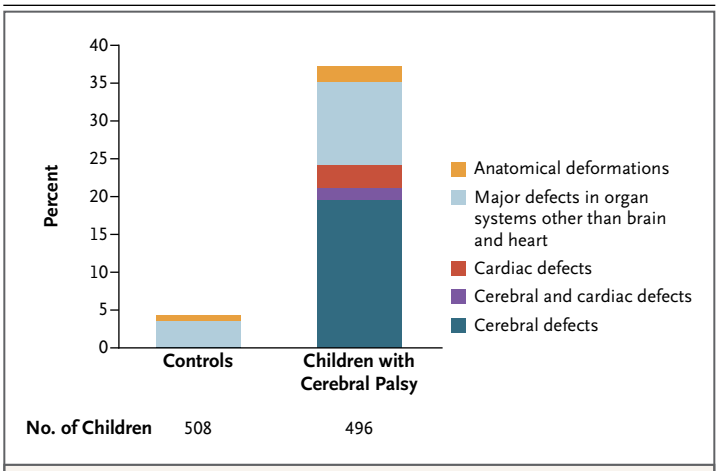

Figure 3. Types of Major Birth Defects in Singleton Children with Cerebral Palsy Born at a Gestational Age of at Least 35 Weeks, 1980–1995.

Reviewing population-based studies that involved neuroimaging in a majority of children with cerebral palsy, Reid et al. concluded that structural brain malformations were present in approximately 11% of those children and in approximately 13% of the subgroup born at a gestational age of at least 37 weeks.[41] These data do not include children who had microcephaly but no recognized structural abnormality of the brain. The brain malformations were diverse, but a cluster of identified forebrain malformations, especially lissencephaly, pachygyria, and polymicrogyria, were associated with congenital microcephaly.[40]

PRENATAL FACTORS ASSOCIATED WITH BIRTH DEFECTS AND CEREBRAL PALSY

FETAL GROWTH RESTRICTION

Marked fetal growth restriction is associated with an increased risk of cerebral palsy.[29,42] It is often assumed that growth-restricted fetuses are especially susceptible to asphyxial injury at birth and that birth asphyxia is the link between growth restriction and cerebral palsy. Large population-based studies have failed to confirm this hypothesis,[29,43,44] however, and in a population-based study, brain imaging in growth-restricted children with cerebral palsy did not suggest global hypoxia–ischemia.[21]

If it is not birth asphyxia that makes growth-

restricted infants susceptible to cerebral palsy, what is it? Neonates with poor growth are more likely to have birth defects than those with normal growth,[29,45] and conversely, infants with birth defects are more likely to have restricted growth.[46] Among infants with fetal growth restriction, the presence of major birth defects marks those at special risk for cerebral palsy.[29]

THROMBOTIC STATES

Low blood flow in the placenta, brain, or other organs confers a predisposition to clotting, and the combination of inflammation and low blood flow increases the risk of thrombosis. Thromboembolism, vascular disruption, and major hemodynamic shifts can contribute to malformations, including congenital limb amputation and gastroschisis.[47,48] When such events occur relatively early in pregnancy, they can cause brain lesions, and later in pregnancy, they can cause cerebral infarction in a vascular territory. Perinatal stroke due to such cerebral infarction is a common cause of hemiplegic cerebral palsy, the most common type of cerebral palsy in children born at or near term. An article about thromboembolism and congenital malformations postulates that several sporadically occurring ophthalmologic syndromes originate from thromboemboli or abnormal hemodynamics.[48]

Twins have a higher frequency of malformations[49] and of cerebral palsy[50] than singletons. The in utero death of one twin, even if it occurs early in gestation, leaves the surviving twin at markedly increased risk for cerebral palsy.[50,51] Vascular anastomoses in the twin placenta, disseminated intravascular coagulation, embolization, and marked hemodynamic changes have been suggested as mechanisms of antenatal cerebral injury in the surviving twin.

PLACENTAL CONDITIONS

Pathologic processes in the placenta are associated with cerebral palsy,[14,44,52] growth restriction,[52,53] and some birth defects.[54,55] Embolization from the placenta near the time of delivery, a period characterized by hypercoagulability, has been suggested as a cause of perinatal stroke. A left-sided predominance of brain lesions has been observed in cases of perinatal stroke,[56] perhaps a result of thromboemboli and the underlying vascular anatomy. We are aware of no controlled studies of the role of the placenta in perinatal stroke.

Of the placental conditions associated with an increased risk of both cerebral palsy and birth defects, fetal thrombotic vasculopathy is especially notable, since it is linked with term stillbirth,[57] fetal growth restriction,[58] birth defects,[54,55] neonatal encephalopathy,[59] and cerebral palsy.[14] In a case series of term births, placental pathological investigation of infants with perinatal neurologic abnormalities showed that of four infants with perinatal strokes, three had placental evidence of fetal thrombotic vasculopathy.[60] In addition to its usefulness in identifying thrombotic or inflammatory processes, the placenta can be tested for specific intrauterine infections such as cytomegalovirus, which is also a known cause of cerebral palsy.

GENETIC FACTORS

Many birth defects have a genetic cause. For some infants with cerebral palsy, a genetic component has been suspected because a sibling also has the disorder.[61] The development of large population-based data sets has facilitated efforts to investigate familial aggregation. One population-based study showed that the risk of cerebral palsy was increased by a factor of 11 among singletons born at term who had an affected older sibling and by a factor of 15 among twins who had an affected co-twin.[62] The similar risk for twins regardless of whether the co-twin was the same sex indicates that the environment also plays a role.

A variety of techniques[63-66] have confirmed the presence of a genetic component in many cases of cerebral palsy. Such studies are still in their infancy, but the findings in cerebral palsy, as in other neurodevelopmental disabilities, already indicate enormous complexity, with the same mutation producing a spectrum of neurodevelopmental outcomes and with marked genetic heterogeneity among similar phenotypes.[15,30,31]

PREDOMINANCE OF PRENATAL RISK FACTORS

Studies of infants in representative populations indicate that disordered prenatal development predominates over adverse birth events as an antecedent of cerebral palsy in term or near-term neonates. Most of the factors associated with an increased risk of cerebral palsy are themselves etiologically diverse.

The chief antecedents of cerebral palsy at or near term are not single-cause events or injuries

occurring at a specific point in time; instead, they are disordered developmental processes, as evidenced by birth defects, poor fetal growth, genetic mutations, and placental disorders. Known prenatal factors may directly increase the risk of cerebral palsy or may interact with other exposures or intrapartum events to increase the risk.

Assessment of the time of onset of brain disorders underlying cerebral palsy is not straightforward because abnormalities that occur early in pregnancy influence the likelihood of later complications. Adverse events such as threatened abortion (i.e., symptoms indicating the threat of spontaneous abortion) in the first trimester are associated with increased complications later in pregnancy, during birth, and in the newborn period.[67-69] Malformations of the cerebral cortex are more common in babies who have birth complications than in controls.[70] In the Collaborative Perinatal Project, 35% of infants with clinical signs of birth asphyxia had a major malformation,[5] as did a third of children with neonatal seizures.[33] Even placental abruption, the most common catastrophic event at birth, has important antecedents, including placental inflammatory and vascular disorders.[71] It is not easy to know whether delivery complications are causes of cerebral palsy, proximal results of prior causes, or both.

HETEROGENEOUS ENTITIES

Cerebral palsy and its major predictors — birth defects, fetal growth restriction, and neonatal encephalopathy — are not etiologically uniform, and the effect of each predictive factor is likely to be related to its specific cause. For example, the implications of low Apgar scores resulting from transient airway obstruction or maternal medication differ from those due to irreversible cerebral injury.

Fetal growth restriction has a variety of causes. Normotensive fetal growth restriction is more closely related to the risk of cerebral palsy than is growth restriction associated with preeclampsia, and normotensive growth restriction combined with birth defects is most strongly associated with cerebral palsy.[29]

When asphyxial events during birth are sufficiently severe to cause irreversible brain damage and cerebral palsy, the infant will have encephalopathy in the newborn period. Nonasphyxial factors can mimic birth asphyxia and cause a similar encephalopathy in the newborn. Therapeutic hypothermia decreases the risk of death or cerebral palsy in neonates with encephalopathy but benefits only a minority of them.[72] Most cooling studies have excluded infants with major malformations identified in the first hours of life, and some have excluded infants with markedly restricted growth. Whether the cause of encephalopathy in the newborn influences the response to therapeutic hypothermia is unknown, and this question warrants investigation.[73]

IMPLICATIONS

The considerable evidence that prenatal factors have an important influence on the risk of cerebral palsy has a number of implications. If the greater likelihood of major birth defects following fetal growth restriction is associated with cerebral palsy, then the ability to offer a reliable prognosis and anticipate the need for special management may be improved by thorough evaluation of a growth-restricted fetus or neonate for birth defects. If the copresence of birth defects links poor fetal growth to cerebral palsy, then earlier delivery is unlikely to prevent cerebral palsy in growth-restricted infants.

Factors that contribute to both birth defects and poor prenatal growth, such as intrauterine infections, teratogens, and certain genetic syndromes, should come under special scrutiny. The possible commonality of biologic mechanisms in several developmental disorders indicates a need for studies that examine the joint occurrence of such disorders in individuals and in families. Incorporation of data on birth defects in such studies may aid in further defining the phenotype and provide information about when the neurodevelopmental program went awry.

Information from placental investigations and rapid-turnaround microanalyses of biochemical and genetic markers are likely to inform future evaluation and treatment of neonates with restricted fetal growth or neurologic abnormalities. Current experimental models of neonatal encephalopathy and of cerebral palsy probably do not adequately simulate the clinical situation for most infants with those outcomes. It now seems likely that the placenta plays a role in brain development, and the important first steps have been made in developing animal models that allow the investigation of specific relationships between the placenta and the fetal brain.[74]

Litigation related to cerebral palsy has been common and very costly in the United States and elsewhere in the developed world. A common

allegation is that medical caregivers fail to prevent cerebral palsy by not responding or by responding too slowly to heart-rate patterns on electronic fetal monitoring during labor. However, cerebral palsy has not been shown to be preventable by a response to electronic fetal monitoring.[2,75-78] A 2014 publication stated, "The American College of Obstetricians and Gynecologists, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and the Society of Obstetricians and Gynaecologists of Canada have acknowledged that there are no long-term benefits of EFM [electronic fetal monitoring] as currently used."[79]

In the past, assumptions about an asphyxial cause of cerebral palsy have led to an increase in surgical deliveries, harmed maternity services,[80] and blinkered research. It is now evident that in advantaged countries, most cases of cerebral palsy in term or near-term neonates must have other explanations. Clinical investigations allied with research in genetics and genomics, teratology, and developmental neuroscience are likely to lead to a greater understanding of cerebral palsy and other neurodevelopmental disorders.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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