Prenatal Origin of Hemiparetic Cerebral Palsy: How Often and Why?

"The prenatal period is dangerous: antenatal mortality is around 70%. Postnatal major or minor problems resulting from prenatal disturbances afflict nearly 10% of those who survive embryonic and fetal life. The nervous system is often a target. Statistical data suggest that 25% of conceptions are affected by developmental disturbances of the central nervous system." 

The first report concerning prenatal brain damage may have come from the neuropathologic investigations of Virchow in 1868. Since then there has been a slow accumulation of neuropathologic and clinical evidence that some brain disorders, including some cases of hemiparetic cerebral palsy, have their origins prenatally. With the advent of neuroimaging the pace at which such evidence has been reported has accelerated. The description by Scher and colleagues of six full-term neonates with intracranial lesions dated by ultrasonography to pathologic processes occurring before the onset of labor is an example of the application of neuroimaging techniques to the question of when cerebral lesions originate.

Christensen and Melchior pointed out that "Any post-mortem study of neuropathology in hemiplegics is bound to be unrepresentative as most of these patients survive for a long time." An important advantage of neuroimaging, and especially of ultrasonography, is that it provides a noninvasive, apparently risk-free, and widely applicable approach to obtaining information on brain structure relatively near to the time of presumed pathogenetic events.

This commentary touches briefly on hemiparetic cerebral palsy, on what fraction of it occurs prenatally, and on a little of what we know about the mechanisms by which it may arise.

HEMIPARETIC CEREBRAL PALSY

Hemiparesis, or unilateral spastic paresis usually affecting the arm more than the leg, is the disability in 20% to 40% of children with cerebral palsy. The birth weight distribution in hemiparetic cerebral palsy is less skewed toward low weight than in other forms of cerebral palsy (Grether JK, Cummins SK, Nelson KB, unpublished data), although during recent years the prevalence of hemiplegia has increased in infants of low birth weight. Unlike most other forms of cerebral palsy, congenital hemiparesis is associated with lower socioeconomic status; that association, in turn, may be related to higher parity and to prior reproductive losses, although it is not known how these factors are connected.

HOW OFTEN IS HEMIPARETIC CEREBRAL PALSY DUE TO PRENATAL INJURY?

Unfortunately, most reports documenting the prenatal occurrence of hemiparesis and of other forms of cerebral palsy are not informative as to what fraction of the disorder is due to problems arising before birth, because these reports do not contain information on the number of cases of the disorder arising in the same population that were not prenatal in origin.

Two studies of early onset hemiparesis in Swedish populations offer evidence that disability arose prenatally in a majority of the children who were born at term. In preterm infants, hemiparesis often may be related to early postnatal events or to an interaction between prenatal and perinatal factors.

Studies are now in progress of imaging in preterm babies in population-based studies. It is reasonable to hope that in the near future there will be imaging studies that sample populations of full-term babies as well, with later ascertaining of neurologic status in those children. Such studies will provide information on the proportion of infants with later neurologic disabilities who have prenatal brain lesions evident by neonatal ultrasonographic examinations.
WHAT ARE THE POSSIBLE PRENATAL CAUSES OF HEMIPARESIS?

Evrard et al summarized prenatal brain-building as follows: the major steps of the first half of gestation are formation and multiplication of neurons, their migration, and the regional development of the cerebral vesicles. In the second half of gestation, growth and arborization of neuronal processes, development of synaptic connections, and myelination and gliogenesis occur. The major lesional mechanisms of the second half of gestation are residual disturbances of histogenesis, interference with circulation of spinal fluid leading to hydrocephalus, ischermias, infection, trauma, and minor cortical disturbances of growth and differentiation.

Given the complexity of the processes of generating a nervous system, and the dependence of each stage upon the successful completion of the one preceding it, there are many opportunities for development to go wrong. Confident identification of the mechanism by which brain maldevelopment or damage occurs is not necessarily easy, even by means of neuropathologic investigation: "The same cause may lead to different types of lesions, and morphologically identical lesions may be due to different causes. In addition, cause and pathogenesis of fetal brain lesions are often speculative.

In the brains of children with hemiparesis, whether investigated by neuropathology or neuroimaging, there are sometimes wedge-shaped lesions suggesting vascular occlusions. Later findings on computed tomography suggestive of infarction are considerably more common in children with hemiparetic cerebral palsy than in those with other forms of cerebral palsy. Underlying the vascular occlusions (in utero strokes) may be aberrant development of blood vessels, abnormality of blood constituents, vasculopathies, embolic or thrombotic disorders secondary to maternal diseases or those of the fetus or placenta. Perfusion failures may be secondary to maternal disease, cardiovascular collapse, or serious hypoxemia through mechanisms including anaphylaxis, shock of any etiology, or gas intoxication. Direct trauma may involve the fetus, and some authors consider the possibility that trauma without direct injury to the fetus may produce enough release of maternal catecholamines to affect the fetus via vasoconstriction. A variety of disorders of the placenta and cord can affect the fetal brain.

Many series of cases through several decades have demonstrated that congenital hemiparesis more often affects the right side of the body than the left (Grether et al, unpublished work), and some authors have considered the possibility that embolization may account for the excess of left-brain lesions.

Strokes that begin in the first days after birth may be the results of sepsis, disseminated intravascular coagulation, sinus thrombosis, embolization, or unknown factors. Barmada et al. mention the potential relevance of "procedures such as arterial catheterization, surgery, or massive antibiotic treatment which predispose to thrombotic complications." In some children with early hemiparesis, imaging reveals irregular enlargements of the lateral ventricles, other lesions, or no apparent abnormality. The irregular ventricular enlargements may be evidence of white matter necroses in perinatal life. Such features are attributed by a number of authors to perinatal hypoxia or ischemia. But markers of infection appear at least as prominent as markers of perfusion failures in the histories of infants with white matter necroses: Leviton and Paneth point out that the correlates of white matter necroses, where known, often are not factors commonly linked with hypoxia or ischemia such as fetal heart rate abnormalities or low Apgar scores, but include increasing maternal age and housing density (an indicator of low socioeconomic status), congenital malformations, placental vascular anastomoses, maternal and intra-amniotic infection, and twinning.

The association of prenatal brain damage with twinning is of special interest, because the prevalence of cerebral palsy was six times higher in twins than singletons in a population-based study of recent North American births (Grether et al, unpublished data). Ten percent of the cerebral palsy in that cohort was in twins. Twins tend to be low in birth weight and have an excess of congenital anomalies and of obstetric complications including cord entanglement. Shunts through anastomotic vascular connections between twins may produce the transfusion syndrome. Antenatal necrosis of cerebral white matter in twins was associated with polyhydramnios, intrauterine death of one twin, and placental vascular connections, the last-mentioned being the most important factor. When one of a pair of twins dies, disruption of the surviving co-twin may occur due to release of thromboplastin substances or to embolization, shifts in hemodynamics, or other mechanisms. When this occurs early in gestation, before 16 weeks, microgyria and neuronal heterotopia in the surviving twin may result. Mild vaginal bleeding may be the only clinical evidence of the disappearance of one twin. Death of a twin later in gestation can produce destructive lesions in the brain, kidneys, gut, skin, and other tissues of the surviving neonate.
ning ascertained by ultrasonography early in pregnancy is more frequent than at the time of delivery,\(^{31}\) so the explanatory power of the pathogenetic mechanisms in twins may be greater than is evident based on the prevalence of twinning at birth.

The chief point for this discussion is that there are clearly a variety of known mechanisms by which fetal brain injury can occur, and presumably many more awaiting discovery.

**CONCLUSION**

"Consider what must be accomplished during the course of fetal brain development. In effect, in a few months the entire work of hundreds of millions of years of evolution must be reached... Tens of billions of neurons must be born... These new cells must find their way to their anatomical destinations, sometimes moving over substantial distances in an embryo that is constantly changing in form... Once the cell is fixed in place, the axon must find its way to its own destination... They must not only get where they are going and make a connection, but they must avoid making any number of other connections that they might wrongly make in places they pass. Each nerve cell must develop one or more of at least a dozen neurotransmitters... The product of that miracle is the most complicated object in the known universe, a human brain.

In this "Decade of the Brain," we can anticipate the emergence of a great deal more information about how the nervous system develops, prenatally and thereafter, and how and when that development can go awry. That information will come from laboratories, clinics, and nurseries. Neuroimaging of the infant brain, a subject now producing a rich harvest in journals of pediatrics, neurology, radiology, and obstetrics, will contribute important new information about the processes of brain development in our species, the timing of derailment from the normal course of brain development, and some aspects of pathogenesis. Neuropathology and the enormous flowering of new approaches in the basic and clinical neurosciences will help in explication of the mechanisms of maldevelopment and early injury. And we can hope that identification of mechanisms will allow us to develop strategies to prevent at least some of the problems leading to prenatal damage of the developing human brain.

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**REFERENCES**

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**COMMENTARIES**

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PROGRESS IN PEDIATRIC PHARMACOLOGY

The survey by the Pharmaceutical Manufacturers Association has identified 114 drugs and vaccines that are being developed specifically for pediatric use. . .

• The 114 medicines involve 127 clinical testing research projects, since some are being tested for more than one use. An example is Prokine, a colony stimulating factor being tested by Hoechst-Roussel and Immunex for two kinds of blood disorders, for cancer, and for bone marrow transplantation.

• 56 companies are involved in these research projects, a very broad base of companies that again, I think, reflects the strong research capabilities of the private sector.

• Nearly two-thirds of the projects are in the final stages of development: 45 are in the Phase III human clinical tests and another 35 are at the Food and Drug Administration for review.

• Fully a quarter of our research projects—32 to be exact—are for rare diseases and are designated as orphan drugs on the chart.


NOTED BY J.F.L., MD