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Causative Factors in Cerebral Palsy

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Abstract: Causative factors in cerebral palsy (CP) vary to some degree according to gestational age group and clinical CP subtype. Such catastrophes of birth as placental abruption, cord prolapse, and uterine rupture sharply heighten risk of CP. These conditions are fortunately uncommon, and are sometimes not survived; individually and collectively they account for only a small proportion of CP. Among other factors associated with increased risk of CP are prematurity, intrauterine exposure to infection or maternal fever in labor, ischemic stroke, congenital malformations, atypical intrauterine growth (restricted or excessive for gestational age), and complications of multiple gestations. Although any 1 factor, if severe, may be sufficient to cause CP, more often it is the presence of multiple risk factors that overwhelms defense mechanisms and leads to CP. The contribution of genetic vulnerabilities that interact with environmental stressors is an emerging aspect of our understanding of causative factors in CP.
Key words: cerebral palsy, prematurity, perinatal stroke, maternal fever in labor, placenta

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In 1955, obstetricians Eastman and DeLeon[1] noted that, "whereas our obstetrical literature rarely mentions cerebral palsy, the literature of cerebral palsy abounds with statements that the etiology of the disease is chiefly obstetrical." With that introduction, Eastman and DeLeon presented one of the first controlled studies of causative factors in cerebral palsy (CP), finding that:

- Although preterm infants are at high individual risk for CP, the majority of CP arises in infants born at term.
- Placental abruption was more common in children with CP, but of the 96 children with CP they studied, only 2 were born after frank abruption. Abruptio placentae and cord prolapse are dangerous to infants, but are uncommon and sometimes not survived; these conditions do not contribute a major share of CP.
- Half of term infants who developed CP were in good condition in the delivery room, with none of the findings usually taken to indicate birth asphyxia, such as respiratory depression, hypotonia, poor color, or abnormal cry. (The Apgar score was not described until 2 y later.)
- There were more congenital anomalies in infants who developed CP than in controls.
- Babies born to women who were febrile in labor had 7 times more CP than infants of women who were not febrile.

These observations, published more than half a century ago, anticipated many of the results of later controlled studies and made it clear that clinically defined birth injury or birth asphyxia accounted for only a small minority of CP. In addition, this study recognized several nonasphyxial causal factors in CP.

From the earliest days of recognition of CP, in fact, it was known that a number of causative factors, including prematurity, infection, and complications of multiple gestations, could lead to CP. It was known on the basis of neuropathologic examination that ischemic arterial infarction of brain (stroke) was not rare in newborn infants. It was also recognized that many children with CP had experienced none of these causative factors, and that many children with one or more causative factors did not turn out to have CP. It required large controlled multivariable studies, of which Eastman and DeLeon presented the first impressive example, to take us the next step.

This review will examine the evidence concerning causative factors for CP, as these are known in early 2008 in studies of good medical quality of evidence.

What Do We Know About Causes of CP and How Do We Know it?

After Eastman and DeLeon there were a succession of studies using maternal and birth information collected before outcome in the child was known. These studies in representative samples, many of them population-based, first appeared in the 1980s, starting with those of Fiona Stanley and her colleagues in Western Australia. Then followed the Collaborative Perinatal Project and studies in California, Sweden, and Victoria and South Australia. Many of these used large regional databases to ascertain outcome, and 1 group of studies was based on a large health maintenance organization.

Most of the recent studies have been analytically more sophisticated than their predecessors. Recent investigations have incorporated neuroimaging information, which has added importantly to our knowledge of underlying pathobiology (see Inder, this volume). It is these large methodologically careful studies that bring us to our current understanding of causes of CP, a better though still very incomplete state of knowledge.

Many papers have entered the literature in which causes of CP were assigned without controlled study, a subjective procedure that allows investigators to state causes according to their own expectations and assumptions. In what follows, uncontrolled studies and those employing retrospective data ascertained after disability in the child was identified, which entails the possibility of recall bias, are not included.

Controlled population-based studies are necessary for the identification of major causes of clinical disorders, and for studies of prognosis. Such studies do not, however, identify rare conditions whose recognition requires uncommon procedures or highly specialized knowledge, such as the Worster-Drought syndrome or DOPA-responsive dystonia, although the latter is important to recognize because of its responsiveness to treatment.[2] There are trade-offs of large and generalizable samples versus specialized focus, and studies that optimize each are needed to provide a 3-dimensional picture.

Several themes will emerge from this review: dominant causes of CP differ somewhat according to gestational age and clinical CP subtype. Although often discussed as if they were causes of later disability, low Apgar scores and respiratory depression and other signs of neurologic depression in the newborn infant are results of their own antecedents, and if

adequate resuscitation is available are not causes in themselves. These signs are not specific to asphyxial etiologies and do not serve to establish the cause of depression in the neonate. A single severe exposure such as uterine rupture or massive abruption can be sufficient to cause CP, but much more often it is not a single cause, but rather multiple concurrent risk factors that precede CP. And multiple risk factors markedly increase risk.

Controlled studies, neuroimaging[3] and clinical,[4–6] based on populations provide the best available estimates of the proportion of CP accounted for by each etiologic factor (Table 1).

Causative Factors not Uniform in Different CP Subtypes and Gestational Ages

Vulnerabilities to CP differ at different gestational ages, and a somewhat different range of causative factors is apparent for different CP subtypes.[7] In-term and near-term infants, hemiparetic (1-sided) and quadriparetic (4-limb) CP are the most common clinical subtypes, whereas in preterm and very preterm infants spastic diplegia (legs affected more than arms) is the predominant form of spastic involvement.

TABLE 1. Estimates of Proportion of Cerebral Palsy in Term and Near-term Infants Attributed to Major Causes in Population-based Studies

Neuroimaging based[3]	
Perinatal ischemic stroke	22%
Congenital malformation	15
White matter disorder	12
Hypoxia-ischemia	5
Clinical studies	
Intrauterine exposure to inflammation[3,4]	11%-12%
Birth asphyxia[5]	6
Complications of multiple birth[6]	5

At the head of the list of causes of hemiplegic CP, according to neuroimaging studies,[8] are perinatal stroke and congenital malformations. Hemiplegic CP is due to a focal, or sometimes a multifocal, pathology, and not the result of generalized hypoxia-ischemia.

Spastic diplegia, the CP subtype that is most common in premature infants, can also occur in infants who were products of pregnancies that went to term. Causal factors for spastic diplegia include evidence of intrauterine infection, premature rupture of membranes, and multiple gestation.[9] Several studies have found preeclampsia to be "protective" against CP. It is still unclear whether preeclampsia is just less toxic than inflammation as a factor leading to preterm birth, or there really is some factor associated with preeclampsia or its treatment that is beneficial—such as perhaps magnesium sulfate administered for preeclampsia.[10]

Quadriplegic (4-limb) CP can be caused by any pathology that inflicts bilateral and widespread damage to brain. Spastic quadriplegia, especially if accompanied by movement disorder, is the form of CP that results from global hypoxic-ischemic events,[11] although such events are not the only possible causes of this clinical syndrome.

Birth Asphyxia: What it Does and Does not Cause

Birth asphyxia can cause CP. It has been demonstrated repeatedly in controlled population-based studies, however, that interruption to oxygen supply to the fetus does not account for most CP. The term "chronic hypoxia" is sometimes employed but is vague and unverifiable; if it is used to indicate the presence of placental vascular disease, such vasculopathy might interfere with oxygen transport, but would be likely to interfere with

production and transport of many other molecules in addition to oxygen.

Over the decade of the 1990s, there was a 90% decrease in diagnoses of birth asphyxia as recorded on vital documents in California, where 1 in 9 American children is born.[12] There was no change in CP rate in children born in a region of California in that period. The decline in birth asphyxia diagnosis agrees with decline in very low Apgar scores in Western Australia without a decrease in the CP rate. Such observations should stimulate questioning of previous assumptions relating birth asphyxia and CP.

More direct evidence of the contribution of birth asphyxia to CP comes from large controlled studies in populations. In agreement with Eastman and DeLeon, half or three-quarters of infants with later-diagnosed CP were not markedly depressed in the newborn period.[13] Furthermore, of those infants who were depressed or manifested neonatal encephalopathy, a majority did not have a recognized asphyxial precursor to their depression. In a population-based American study, only 6% of children with CP had had a recognized birth complication capable of interrupting oxygen supply to the fetus.[4] Among term-born children in a well-planned study in a regional cohort who had encephalopathy and seizures, acidosis, and renal dysfunction in the neonatal period and later 4-limb CP, only a third had recognized intrapartum asphyxial events that seemed to account for this clinical sequence.[14] In the remainder of affected infants, despite the similarity of the clinical features, the cause or causes was not apparent. This study did not include placental pathology. Similar findings are noted in several studies of antecedents of severe depression in term infants who were candidates for hypothermic therapy for "hypoxic-ischemic encephalopathy."

Neonatal encephalopathy is an inevitable intermediary between asphyxial birth and long-term neurologic disability.[15] Infants who have undergone acute asphyxia during birth, sufficient to produce irreversible brain injury, do not rapidly recover normal neurologic and systemic status. Of term infants with encephalopathy, only a minority had experienced recognized compromise to oxygen flow around the time of birth. Some other candidate conditions have been identified, including maternal thyroid abnormalities and maternal fever in labor.[16] Thus, the clinical picture of respiratory and neurologic depression in the newborn is not specific as to etiology. A low Apgar indicates that an infant is ill, and is not in itself informative as to the cause of that illness. Chorioamnionitis, for example, is known to increase risk of low Apgar scores, meconium in the amniotic fluid, and neonatal seizures,[17,18] so these signs can be—often are—related to infectious or inflammatory rather than asphyxial conditions.

The CP that birth asphyxia does cause is spastic 4-limb involvement, spastic quadriplegia[11]; there are other potential causes of that syndrome. Global hypoxia-ischemia is not a likely cause of hemiplegic CP or spastic diplegia. Global hypoxia-ischemia is not a plausible cause of CP in an infant who did not manifest encephalopathy in the newborn period.

Interventions based on the birth asphyxia hypothesis have not led to a decrease in CP. An important example is the repeated observation that electronic fetal monitoring, introduced in the hope of recognizing and intervening early in a developing asphyxial state, has not been followed by a reduction in frequency of CP.[19] This disappointing SAGA is summarized by the title of one review, "Birth can be a hazardous journey: electronic fetal monitoring does not help."[20]

Unfortunately, although it would seem straightforward to prevent the small share of CP that is related by asphyxial events, that has not proven to be so. This fact suggests that we have been operating,

clinically and experimentally, with too simple a conceptual model. There is clinical and experimental evidence that nonasphyxial factors can be sufficient antecedents to CP. In addition, asphyxia-ischemia can interact with other causal factors such as inflammation, the joint occurrence of both further multiplying risk. Other causative factors may also interact with these. Thus, hypoxia-ischemia may arise at a cellular level downstream in a pathobiologic process that began with other instigators, and the clinical features may not distinguish primary from secondary or tertiary effects.

The question is seldom asked, if there was asphyxial-ischemic injury as part or all of the pathogenesis of depression in the neonate, when did that asphyxial injury occur? That question is critical to development of effective strategies for prevention, as an acute interruption of oxygen supply to the infant before or during birth would probably require very different action for primary prevention, as compared with a defect in perfusion or cellular response far down the causal chain.

Abnormalities in the fetus can contribute to an aberrant process of labor, as exemplified by the observation that children with cortical malformations much more frequently than others experienced "intrapartum complications, which could lead to the misdiagnosis of hypoxic-ischemic encephalopathy."[21]

An intriguing observation in a study of Wu et al[22] raises questions about the assignment of asphyxial etiology based on neuroimaging findings. Chorioamnionitis was most tightly linked with CP risk in infants whose neuroimaging studies were read as indicating "hypoxic-ischemic brain injury."[22] Perhaps the downstream consequences of insults of varying etiology can produce similar imaging findings, that is, these imaging findings may, like the clinical signs of neonatal depression, not be etiologically specific.

Prematurity

Birth too early in gestation is a very important causative factor for CP, risk per infant being increased up to 100-fold. Preterm and very preterm birth are relatively uncommon among all births, however, so prematurity contributes half or less of CP. The CP that arises in very prematurely born infants is commonly spastic diplegia, and the underlying brain pathology as explored by neuroimaging is white matter disorder.

Intrauterine infection or inflammation and prolonged rupture of membranes are important antecedents of preterm birth, and also of CP in prematurely born children. A recent report indicates that fetal exposure to a variety of viruses may be associated with hypertensive disorders of pregnancy, a risk factor for CP, and cytomegalovirus was also associated with risk of birth before term,[23] an example of a potential chain of causal links in which the cause of preterm delivery may also be a cause, in addition to the prematurity itself, of brain injury in the early-born fetus.

In addition to infection or inflammation, risk factors for premature birth include previous preterm birth, black race, low maternal body mass index, vascular disease, and multiple gestation.[24] Medical indications for preterm delivery include preeclampsia or eclampsia and fetal growth restriction. A genetic contribution to preterm birth is estimated to account for 20% to 40%.

Atypical Intrauterine Growth

Babies who are small for dates at birth are at increased risk for CP, a relationship often cited. Equally striking, and much less often cited, is the fact that babies who are large for dates are also at increased risk: there is a U-shaped curve, with heightened risk associated with growth abnormalities at both ends of the scale.

A host of growth factors can influence size at birth, some of them after only a

brief early exposure. Clinical characteristics of mother or child that are associated with fetal growth restriction include chromosomal abnormalities (infections such as TORCH agents, malaria, HIV), preeclampsia, systemic maternal vascular disease, or thrombophilia. It is possible experimentally to produce growth retarded fetuses by clamping uterine arteries, but it is unknown whether this procedure models a mechanism that occurs with substantial frequency in human fetal growth restriction.

Size larger than the norm for gestational age is also associated with risk of CP. Some of this excess risk may be related to size per se leading to problems in delivery. The classic risk factor for macrosomia is maternal diabetes, although in most studies diabetes itself does not seem to increase risk for CP in the infant. Both excessively small and excessively large babies are at higher risk for perinatal stroke than infants near the mean of weight for dates.[25]

Cloned animals sometimes die before birth with a "too big syndrome" that includes a placenta of excessive size. Assisted reproductive technologies seem to be associated with a small but significant increase in risk of imprinting disorders such as Beckwith-Wiedemann syndrome, which is associated with large fetal size, suggesting that epigenetic mechanisms may sometimes be associated with excessive fetal growth.[26]

Infection, Inflammation, and Maternal Fever in Labor

Congenital TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes virus, and other microorganisms including those of hepatitis B, syphilis, and HIV) and streptococcus B can be transmitted from mother to infant, affect the brain of the infant, and produce congenital motor disability, CP. What is the evidence that microorganisms, or factors associated with them, can cause CP without known invasion of the infant brain?

It is more than half a century since Eastman and DeLeon reported that women who were febrile in labor had babies with 7 times the rate of CP as women not febrile during delivery.[1] In data of the National Institutes of Health Collaborative Perinatal Project (NCPP), women febrile during pregnancy with urinary-tract infections had infants whose tested intelligence was lower, even after adjustment for socioeconomic factors. Gilles et al[27] followed these findings with experimental evidence of white matter abnormalities in the brains of kittens exposed prenatally to infection.

Also in NCPP data, routinely performed examination of the placenta revealed that moderate or severe inflammatory infiltrates in umbilical cord, were associated with heightened risk of CP both in term and preterm infants; in the years of the NCPP, survival of preterm infants was chiefly limited to those not severely preterm. Infants exposed in utero to inflammation had lower Apgar scores.[28] This observation has been confirmed in many subsequent studies.

In a population-based study in northern California, evidence of maternal infection or fever during the admission for delivery was associated with risk of CP in infants of normal birth weight, and with admission to a neonatal intensive care unit, neonatal seizures, and meconium aspiration. A recent paper agrees that meconium passage is commonly due to inflammatory, not asphyxial, factors.[18] Most infants exposed to inflammation or fever in utero did not experience prolonged rupture of membranes or sepsis in the newborn period.

There are now many other studies regarding term and near-term infants, all consistent in finding an association of maternal infection or fever with low Apgar score, neonatal encephalopathy and seizures, and with CP risk. The evidence is

less consistent, but also dominantly positive, concerning the association of inflammatory indicators with CP in very preterm infants. Study of this association in very premature infants is plagued by uncertainty about how best to deal with the important predictor, gestational age. Very premature babies often experience postnatal episodes of sepsis or suspected sepsis that complicate interpretation of the relationship of intrauterine events with long-term outcome.

There has been little systematic study of infectious or inflammatory maternal conditions that occur in pregnancy but before the admission for delivery as risk factors for CP.

Repeated observations, then, document that intrauterine exposure to indicators of inflammation are linked with CP risk, and that this is a common cause of low Apgar scores, other signs of neonatal depression, and CP risk. Vulnerability of the very young brain to inflammatory mediators is evidenced by the fact that administration of interferon-α, an inflammatory cytokine given to shrink life-threatening hemangiomas, has been followed by development of spastic diplegia in infants less than a year old, but not in older children or adults.[29]

As chorioamnionitis and perhaps other infections seem to be a common antecedent to encephalopathy in the neonate and to later CP, should there be aggressive efforts to detect and treat infection? Should antibiotic use be more widespread in pregnancy? Willoughby and Nelson[30] have discussed reasons for caution: identification of infecting agents is difficult but necessary if treatment is to be effective. Placental infection frequently involves multiple organisms that would require different therapeutic agents. Antibiotics are not necessarily free of neurologic risk; for example, metronidazole, a radiation-sensitizing antibiotic used in a number of trials for prevention of preterm birth, can cause an encephalopathy. Administration of a number of antibiotics can affect cytokine, prostaglandins, nitric oxide, and other systems relevant to infant brain development. The possibility of unintended consequences is real, so that randomized trials of antibiotic interventions that include observations of the infant at least through the neonatal period are needed as the necessary basis for responsible action.

Perinatal Ischemic Stroke

Perinatal stroke is a cerebrovascular event occurring during fetal or neonatal life before 28 days after birth. As used here the term excludes hemorrhagic stroke. The separation between ischemic and hemorrhagic lesions can be difficult as ischemic lesions can undergo secondary hemorrhage after reperfusion, and venous infarcts, also excluded by definition, are often hemorrhagic.

Arterial ischemic stroke in the perinatal period has been recognized as a major cause of CP only in recent years, as the use of computed tomography and magnetic resonance imaging have been applied with increased frequency to infants and young children. The diagnosis of perinatal stroke can be suspected but not established in surviving children without such imaging procedures because clinical signs of stroke in the newborn period are variable, nonspecific, and often absent. Cranial ultrasonography is not a sensitive test for stroke. The frequency with which stroke is detected, and therefore the observed prevalence, are also related to the frequency of use of imaging procedures. In a study in which magnetic resonance imaging was relatively often employed, unilateral strokes were identified in 1:2300 term infants during the nursery period.[31] Not included in that study, about a third of strokes are bilateral and many perinatal strokes are not recognized until after the newborn period.

Newborn infants with stroke seldom display asymmetrical movement or strength, as would older children and adults. The most common finding to lead to imaging, and thus to diagnosis, is neonatal seizures. There may be apnea, hypotonia, or other nonspecific signs. Many infants appear well between seizures, but some display neurologic depression and encephalopathy and received diagnosis of "birth asphyxia" or "hypoxic-ischemic encephalopathy." Vasculopathy in the placenta has been linked with encephalopathic manifestations[32] and may underlie the fetal distress and neonatal depression that sometimes is observed in infants with perinatal stroke.

Some infants who appeared neurologically intact as newborns may be diagnosed in later months or years when the child learns to reach with one hand but not the other, indicating a developing hemiparesis, or fails to meet developmental milestones, or experiences the onset of a postneonatal seizure disorder. Retrospective diagnosis in such cases depends on neuroimaging. There has been no test of consensus in the reading of the films on which diagnosis is based, either with respect to neonatally recognized or retrospectively diagnosed stroke.

Stroke is much more common in the perinatal period than during childhood or at any time until late middle life. Thromboses at other sites are also relatively common in the period immediately surrounding birth. It is unlikely to be a coincidence that maternal pregnancy-related stroke is also most common in the few days immediately before or after birth, a period during which coagulation status is maximally altered in both mother and infant.

Known risk factors for perinatal stroke include disorders of mother, placenta, and infant. Normal pregnancy is, overall, a prothrombotic and proinflammatory state. Primiparity, preeclampsia, and a history of impaired fertility and its treatment have been observed in association with perinatal stroke.[33] Maternal or family history of thromboembolic disease, advanced maternal age, obesity, surgery (including surgical delivery), dehydration or shock, and prolonged bed rest are risk factors for thrombosis in the mother, as is a history of maternal migraine.[34] (Migraine and its treatment have not been examined as potential risk factors for stroke in the infant, although headache of migrainous sort is a common complaint in children who have experienced perinatal stroke.) Infection and inflammation are important triggers of thrombosis. Preeclampsia, a maternal risk factor for stroke in the infant, is also associated with risk of ischemic stroke in young women at times remote from pregnancy, and is a risk factor for stroke in the child, and may be associated with thrombophilia.

Both fetal growth restriction and excessive size for gestational age are relatively common in infants with strokes, and a number of authors have observed maternal complains of decreased fetal movements in infants who had perinatal seizures. In the infant, the procoagulant and proinflammatory character of this period, and the high hemoglobin in fetus and neonate, traction on neck vessels, inflammation, dehydration, hypotension, use of intravascular catheters, and importantly the presence and nature of placental thrombotic lesions are associated with perinatal stroke. Thrombotic lesions are the most common finding in placentas of infants with CP.[35] Despite the probable relevance of thrombotic and/or inflammatory vasculopathy in the placenta to the occurrence of perinatal stroke, only a few studies have examined the association of specific findings in the placenta to risk of stroke in the infant.

About half of infants with stroke investigated for thrombophilias are observed to have one or more such findings. Thrombophilias are also common

in the unaffected population, however, so it is necessary to study and interpret these thrombophilias with care. Unless thrombophilic factors are multiple or accompanied by a family history of thromboembolic events, there is no consensus that these provide information that should guide clinical management.

Perinatal stroke has seldom been reported in more than 1 nontwin child in a sibship, so it seems likely that environmental factors play an important role. Despite that, few studies focus on environmental factors in perinatal stroke.

Congenital Anomalies

The consistent observation that children with CP have more congenital anomalies than other children is an important part of the evidence that prenatal factors contribute to CP. Recent studies linking population-based registries for CP and for congenital malformations reinforce previous observations noting congenital malformations of head, clefts of lip or palate, and gut atresias in CP.[36] Other noncerebral anomalies may also be more common.

Multiple Gestation

Twins are at greater risk for CP than singletons, and the risk in triplets is higher still. Many factors have been considered in analysis of this heightened risk, including birth sequence and mode of delivery, presentation, size, size discrepancy, congenital anomalies (more common in monozygotic twins), and many others. The evidence is that 2 factors are predominant in contributing to CP risk in multiple gestation: the tendency of twins and higher order multiple births to be born prematurely, and death of 1 infant. In a study that included more than a million births, the highest rates of CP were in surviving twins whose co-twin was stillborn (4.5%), died soon after birth (6.3%), or had CP (11.8%).[37] CP risk after co-twin death was similar for same-sex and for different-sex pairs (the surrogate for zygosity in a large study in which zygosity could not be determined reliably).

Monozygotic twinning with conjoined circulations in the placenta underlies much of the hazard to a twin or triplet when a co-twin or co-triplet dies in utero. In that situation, the death of 1 twin is followed by vascular collapse in the survivor. If this sequence occurs early in gestation, congenital anomalies can be the result in the survivor. There may be other mechanisms of brain injury in the survivor of a co-twin death, in addition, and anything that harms 1 infant lethally might harm the other sublethally.

The "vanishing" of a twin is fairly common early in pregnancy. Some children who were twins early in gestation may be born as singletons, and bear the consequences of co-twin loss.

Placental Pathology

"The placenta remains a neglected source of discovery."[38] Examination of the placenta can help in the understanding of etiology and can influence workup and perhaps treatment decisions when outcome is adverse.

The relationship of chorioamnionitis with CP risk has been indicated. In material assembled for medicolegal review, the most common placental finding was thrombotic lesions,[35] and the relationship was especially strong if evidence of inflammation was also present.[39] Gross findings indicative of disturbance of uteroplacental circulation, marked perivillous fibrin deposition, and ischemic changes in placental villi were associated with presence of white matter disorder, the lesion commonly underlying spastic diplegic CP.[40]

Chronic villitis, a disorder affecting 5% to 15% of term placentas, is characterized by focal areas of inflammation with mononuclear cells and areas of fibrinoid

necrosis, and often recurs with subsequent pregnancies. When lesions are widely distributed, it is associated with growth restriction, preterm birth, and preeclampsia. The etiology is not well understood but is thought to be related to autoimmune or alloimmune disease.[41]

In the event of fetal or neonatal death and failure to obtain an autopsy, placental examination can be informative.[42]

Once placental tissue has been cut and put into preservative, it can be sectioned and made available to an experienced pathologist long after the delivery. It would be good policy for the placenta of every depressed term newborn to be saved, preferably for immediate examination, but if not, as a resource for investigation of etiology at a later time.

Genetics

Familial aggregation of CP has been reported in populations with high rates of consanguinity, and in a national Swedish database an increased risk for CP was observed in families.[43] Genetic factors can influence CP risk at a number of points along the causal pathway. A number of maternal and pregnancy conditions that are risk factors for CP have a genetic component, including preterm birth, placental abruption, preeclampsia, and chorioamnionitis. Thrombophilias underlying perinatal strokes often have a genetic basis. Genetic variants of certain inflammatory cytokines[44] and an apolipoprotein E variant[45] have been linked with CP risk. Exploratory studies suggest that variants of nitric oxide synthase contribute to CP risk.[46,47] The results of studies to date are compatible with roles in CP pathobiology for inflammation, coagulation, control of blood flow, and function of vascular endothelium in placenta and brain.

Thus, CP can be seen as a common complex disorder, in which many genes contribute to risk and environmental factors and their interaction with genetic characteristics are important determinants of disease occurrence. Only a beginning has been made in studies to examine gene-gene and gene-environment interactions, but much hope for further progress depends on such studies in future.

Multiple Risk Factors

In some cases a single overwhelming factor such as acute interruption of oxygen supply during birth is a sufficient cause of brain injury and subsequent CP. Much more often, however, multiple risk factors converge to overwhelm natural defences. Examples documented in clinical and experimental studies are the interaction of intrauterine exposure to inflammation and asphyxial injury, and the interaction of multiple thrombophilias with one another and with environmental risk factors. The prominence of multiplicity of risk factors in human CP is one reason why many animal experiments do not accurately model the clinical disorder.

The strong contribution of multiplicity of risk factors to CP etiology means that a linear causal chain is often not evident. A causal *web* is a more realistic model, and can mean that results of a given perturbation may be difficult to predict.

Neonatal Encephalopathy

Neonatal encephalopathy is a necessary intermediary between birth asphyxia and CP in term and late preterm infants. All studies that have examined the issue find that only a minority of cases, including those meeting strict criteria for "hypoxic-ischemic encephalopathy" and having CP as the later outcome,[14] can account for only a minority of cases by such "sentinel events" during birth as uterine rupture, cord prolapse, or major placental abruption. What causes the majority of such cases that look clinically identical during the newborn period? This is an important

unanswered question. The study of Badawi and others[16] contain some hints, including maternal fever in labor, maternal thyroid disorder, family history of neurologic disease, and other factors. Incorporation of broader maternal medical history and of examination of placental pathology might advance knowledge in this area, which remains, despite its importance, highly underresearched.

Clues not Pursued

The literature contains a number of observations that have not, to date, been followed up to establish whether these are dead ends or opportunities for new advances. For example, 3 large population-based studies have found lengthy maternal menstrual interval to be associated with CP risk.[48–50] What might this mean? A major cause of aberrant menstrual spacing is polycystic ovary syndrome (PCOS), which is also associated with reduced fertility, obesity, preeclampsia, a procoagulant and proinflammatory state, preterm birth, and need for special care for the infant, all of which are risk factors for perinatal stroke or for CP more generally. In a small randomized trial, treatment of PCOS seemed to improve pregnancy outcome, but CP was not among the outcomes studied. Is PCOS, a common and treatable condition, linked with CP? No study has sought to find out.

Maternal thyroid disease has been related to neonatal encephalopathy in 3 studies (including Ref. 16) in term infants, to CP,[48] to decreased IQ,[51] and to congenital deafness.[52] Antithyroid antibodies are present in 10% of pregnancies[53] and 10% of neonates.[54] No study has sought to examine further the possibility that thyroid hormone level or presence of antithyroid antibodies contributes importantly to encephalopathy in term neonates or to CP, although if present these associations would suggest potential therapeutic interventions.

The literature relating placental pathology to maternal conditions, neonatal status, and long-term outcome in the child is limited in amount and methodologically suboptimal, yet it contains hints of important relationships that have gone largely unstudied to date. It seems that inflammatory and thrombotic lesions, especially when these occur together, are associated with high risk of CP. But there has been to date no study in a large and representative population that connects the dots of maternal and family history, genetic and acquired thrombophilias, maternal and pregnancy history, placental histology, and descriptors of neonatal and later neurologic outcome.

Where to From Here?

The development of large CP registries and regional and national birth cohort studies will make it possible to determine outcome in the child without the need for expensive, difficult, and potentially biased (by nonrandom missingness) follow-up studies. Linkage of these records for the child with maternal medical records will permit investigation of the association of CP with such maternal conditions as PCOS, thyroid disease, and lupus.

Neonatal nurseries often care for ill infants, preterm and term, without knowledge of the placental histology or of maternal or delivery factors that can strongly influence prognosis in the infant, such as presence of maternal fever during labor. More workup of "hypoxic-ischemic encephalopathy" babies would probably be contributory, and more interaction between obstetric and neonatal caregivers to assemble the information needed would enable better differential diagnosis and specific management.

For any term or near-term infant who is markedly depressed in the delivery

room, the placenta should be carefully described and sent to the laboratory. Blocks should be cut in every such case, and the material reviewed by the local pathologist if there is an interested and competent pathologist available; if not, the preserved blocks should be retained for later examination. Once preserved, placental material can be examined at a later time and assembled for consensual reading by expert pathologists. Consensus building on methodology and interpretation of placental pathology and studies relating to outcome in the child are needed.

Conclusions

The literature on the etiology of CP is impressive in its perseverative preoccupation with birth asphyxia despite evidence that this is a minor part of the whole picture, and despite the failure of interventions based on the birth asphyxia hypothesis to lead to effective preventive strategies. Meanwhile, the biology of early brain development and the existing tantalizing hints from methodologically appropriate clinical studies (see above) have gone largely unexplored. We need more studies that look at observable differences between the maternal, birth, and neonatal histories of babies who do and those who do not develop CP, and of babies who do and do not develop conditions antecedent to CP such as neonatal encephalopathy and perinatal stroke. We need to know more about infection, inflammation, and fever and how the link to fetal brain injury could be minimized. Focus on other environmental risk factors including such common factors as inflammation and dehydration that might interact with genetic vulnerabilities is sorely needed, because it will be through management of these environmental factors that important preventive strategies may become feasible.

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