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Perinatal Ischemic Stroke

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Abstract—Perinatal ischemic stroke is not rare in term and near-term infants and is an important antecedent of long-term neurological disability, including congenital hemiplegia (hemiplegic cerebral palsy) and seizure and cognitive disorders. Changes in maternal hemostasis occur in pregnancy and are amplified in the period immediately surrounding birth; stroke and other thromboembolic events are more frequent in both mother and infant in this period. The vasculature and hemostatic mechanisms of placenta as well as brain are likely to be important in the pathobiology of perinatal stroke. Maternal and infant thrombophilias, genetic and acquired, play a role. Rarely is >1 child in a sibship affected, and environmental factors—substantially less studied, to date—are likely to be key determinants of risk. (*Stroke*. 2007; 38[part 2]:742-745.)

Key Words: hemiplegic cerebral palsy ■ perinatal stroke

"A large number of cases of infantile cerebral palsy are caused by the same factors that bring about the majority of cases of cerebral paralysis of adults: tearing, embolism, and thrombosis of cerebral vessels."[1]

The 2 periods of life in which the risk of having a stroke is highest are in the elderly and in the fetus or newborn infant. In both these periods, stroke is associated with heightened risk of death or, in survivors, of persisting neurological disability.

It was recognized long ago on the basis of autopsies in newborn infants that perinatal arterial ischemic stroke (PAS) can occur and is not extremely uncommon. The advent and increasing use of neuroimaging in young children permitted identification of PAS in surviving children and led to recognition of the relatively high frequency of PAS and its high morbidity. Clinical features of stroke in the perinatal age group, risk factors for its occurrence, and natural history, including outcome, are increasingly, although still imperfectly, known.

Why does stroke in the fetus or newborn warrant inclusion at the Princeton Conference, a gathering that focuses on stroke in adults? The freedom of the neonate from comorbidities that feature so prominently in stroke in the adult, such as atherosclerosis, diabetes, hypertension, and smoking, permits a view of the neurovascular processes underlying ischemic stroke in the newborn in relatively pure culture. The potential benefit to the understanding of adult stroke is exemplified by the recognition of homocystinuria in children that preceded recognition that homocysteine levels are related to risk of arteriovascular disease in adults. On the other hand, some features of PAS are unique to this age period; it is these that will be stressed in this brief review.

Definition and Incidence

PAS is a cerebrovascular event occurring during fetal or neonatal life, before 28 days after birth, with pathological or radiological evidence of focal arterial infarction of brain. As used here, the term excludes hemorrhagic stroke, generalized ischemic lesions in arterial border zones, and cerebral venous thromboses. In the newborn, unlike the older child or adult, there are no clinical signs that permit even a presumptive diagnosis of perinatal stroke; recognition rests on neuroimaging.

Estimates of the frequency of PAS vary with the frequency of use of CT or MRI. In a recent population-based study with relatively frequent neuroimaging, unilateral PAS was recognized in the neonatal period in 1 in 2300 term infants.[2] Bilateral strokes are not uncommon, and not all infants were imaged, however, and this prevalence figure does not include children whose PAS was first identified after the newborn period (see below).

Stroke is 17 times more common in the perinatal period than later in childhood or beyond.[3] In the only available population-based study of perinatal stroke that included children whose perinatal stroke was diagnosed after the first months of life,[4] the rate of perinatal stroke was 1:5000, at least as high as the annual incidence of large-vessel ischemic stroke in adults (17 to 23 per 100 000).[5] Thrombosis at other sites also concentrates in the perinatal period.

The Clinical Entity

In the neonate, PAS may present with nonspecific signs including hypotonia, apneas, or neonatal seizures. Unlike older children and adults, the neonate seldom exhibits asymmetry of movement or tone with stroke onset. It is commonly neonatal seizures that lead to performance of an imaging

study and thus to diagnosis. Cranial ultrasonography, the most widely used form of neuroimaging in the nursery period, is not a sensitive detector of stroke. Infants with PAS who have neonatal seizures may appear clinically well between episodes, or there may be other signs of encephalopathy; 5% of children with neonatal encephalopathy in 1 study had had perinatal stroke.[6]

Infants whose neurological status aroused no concern in the newborn period, or who were born in facilities without imaging capability, may be brought to medical attention at the age of 4 or 5 months or later, when asymmetrical hand use or failure of developmental milestones is observed or new-onset seizures appear.[7] These findings may then lead to the retrospective diagnosis of perinatal stroke, based on neuroimaging. Infants with later-diagnosed PAS constitute perhaps a third of the total with perinatal stroke. Although radiological judgments about the presence and characteristic features of perinatal stroke are critical for diagnosis both in the newborn period and later, there have as yet been no studies of interrater reliability in diagnosing PAS diagnosis or in radiological criteria for timing of onset.

PAS is thought to occur before ≈72 hours of postnatal life, but more precise timing is usually uncertain and can be as early as the second trimester. In infants whose stroke predated birth by weeks or months, as determined by histological criteria, there may be neonatal depression with signs suggestive of "birth asphyxia";[8] it would thus appear that encephalopathic signs in neonates with stroke do not establish that the stroke occurred near the time of birth.

Perinatal stroke may result from thrombosis of intracranial vessels or from embolism from another site such as extracranial vessels, heart, umbilical vein, or placenta. Although the site of origin is usually not clearly established, it is suspected that the fetal side of the placenta may often be the source.

PAS has been described chiefly in term or near-term infants. Whether this disorder seldom occurs in very preterm infants or appears clinically different in such infants is unknown.

Hemiplegic cerebral palsy is a common outcome of PAS, present later in 37% of children whose stroke was recognized in the newborn period and in 82% of those with retrospectively diagnosed PAS,[9] in whom emerging hemiparesis was often the finding that led to neuroimaging and thus to diagnosis. If lesions are bilateral, quadriplegic cerebral palsy can result. PAS is probably the most common known cause of hemiplegic cerebral palsy in term and near-term infants, and therefore if a child has congenital hemiplegic cerebral palsy, it is more probable than not that that child had a stroke. Confirmation of the diagnosis depends on neuroimaging.

Children with cerebral palsy attributable to stroke often have additional neurological comorbidities, including seizure disorders that can be intractable to medical therapy, delayed language development, and behavioral disorders. How often cognitive disorders or epilepsy attributable to perinatal stroke occurs in the absence of cerebral palsy is not known. In a population-based study, 64% of children whose PAS was recognized in the newborn period later had at least 1 of these disabilities.[9] Of children whose perinatal stroke was first recognized after the newborn period, 94% later had 1 or more neurological disabilities. In this population, a majority of children who had cerebral palsy caused by perinatal stroke were not recognized to be affected in the newborn period. Thus, the outcome of a pregnancy considered to be at risk for perinatal stroke cannot be established until after the first year of life or after neuroimaging.

Maternal Pregnancy-Related Stroke

Mothers, as well as infants, are especially vulnerable to thrombotic and thromboembolic complications, including stroke, during pregnancy and the puerperium. A recent study in a national inpatient sample[10] reported risk factors for pregnancy-related stroke to include postnatally identified infection (odds ratio [OR] 25); migraine (OR 16.9); thrombophilia, including history of thrombosis and the antiphospholipid syndrome (OR 16.0); systemic lupus (OR 15.2); heart disease (OR 13.2); preeclampsia (OR 4.4); diabetes (OR 2.5); and smoking (OR 1.9). Migraine may also be a risk factor for stroke outside of pregnancy.

Other studies have identified obesity, relatively older age, bed rest for >3 days during pregnancy, and surgical delivery for risk of stroke in the mother. These risk factors for maternal stroke are consistent with possible relevance of inflammation, faulty vasomotor regulation, thrombophilias, and autoimmune disorders to stroke risk in the mother. Some of these factors may also be relevant to stroke risk in the fetus or infant (see below).

Thrombophilias occurring alone are fairly common and are seldom associated with high risk, but mothers or infants with combinations of thrombophilias, or these plus environmental risk factors, are at sharply higher risk.

A common disorder of women in the reproductive years, polycystic ovary syndrome, is associated with menstrual irregularities, decreased fertility, polycystic ovaries, obesity, and metabolic syndrome including elevated levels of plasminogen activator inhibitor-1, the major natural antifibrinolytic agent.[11] No single feature is required for diagnosis. Three studies in defined populations have observed lengthy or irregular menstrual intervals to be associated with risk of cerebral palsy. In one of these, lengthy menstrual interval, high maternal body mass index, and placental infarction were all risk factors for cerebral palsy.[12] Maternal epilepsy and its treatment increase risk of polycystic ovary syndrome [13] and of neonatal encephalopathy[14] and cerebral palsy.[15] Polycystic ovary syndrome is treatable; could it underlie some proportion of perinatal stroke?

Pathobiology

Normal pregnancy is a procoagulant and proinflammatory condition. Risk of stroke is higher in pregnancy than in the nonpregnant state. The risk of maternal pregnancy-related stroke rises at least 34-fold in the 3 days immediately surrounding birth,[16] when coagulation mechanisms, already activated by pregnancy, ramp up further, in evolutionary anticipation of hemorrhage, which threatens the life of mother and fetus. Unfortunately, the adaptation that lessens risk of bleeding increases risk of clotting.

In the fetus, hematocrit is high, as is blood viscosity, and there is a stage-dependent depression of anticoagulant activity. The placenta has areas of low flow, known by Virchow to

predispose to coagulation. The placenta, which has its own hemostatic mechanisms, is probably an important locus of pathology in PAS. In cases reviewed for litigation because of cerebral palsy in the child, thrombotic lesions were the most common pathology found in the placenta.[17] Expert placental pathologists sometimes observe thrombotic lesions when none were noted in the initial report. Once slides exist, these can be sent for specialist's review.

During birth there may be traction or other injuries to neck vessels, and in the nursery period dehydration, hypotension, infection, and intravascular catheters contribute to risk. The presence of a patent foramen ovale enables clots from the fetal side of the placenta to embolize into the fetus, bypassing hepatic and pulmonary circulations to reach the fetal brain.

In addition to cerebral infarction, thrombosis in other sites, including kidney, heart, aorta, and limb arteries, is more common in neonates than at other times in childhood.

A number of reports describe acquired thrombophilias in women whose pregnancies resulted in the birth of a child with perinatal stroke. Antiphospholipid antibodies can pass from mother to child via the placenta and can alter the placenta itself, changing its function. Although described earlier than inherited thrombophilias, maternal antiphospholipid antibody disorders have been less investigated for their role in PAS, perhaps because of absence of consensus as to which of the several antiphospholipid antibodies are most important for study and because of lack of standardization of assays. The large volume of blood required for assays of antiphospholipid antibodies precludes testing of affected infants in the newborn period, and passively transferred antibodies decline with postnatal age. Maternal levels of antiphospholipid antibodies vary over time, and therefore drawing of maternal blood for testing is appropriate as soon as a diagnosis of PAS is made in the child.

Although the evidence is less than complete or entirely in agreement, it seems likely that maternal and perhaps infant thrombophilias can lead to complications of pregnancy, such as prior fetal death, preeclampsia, abruptio placentae, placental vasculopathy, and fetal growth restriction,[18] which are in turn risk factors for neonatal encephalopathy, stroke, or cerebral palsy. No study yet available covers the entire potentially multistep pathway from parental history or thrombophilia to risk of stroke in the child.

Risk Factors for PAS in the Child

Many studies linking thrombophilias in the child with stroke risk have investigated pediatric stroke in general rather than perinatal stroke specifically. In one of the few studies limited to PAS, Gunther and colleagues[19] found at least 1 of the 6 examined prothrombotic risk factors in 68% of affected children and in 24% of controls. The most common factor identified was a high level of lipoprotein(a), present in 20%. A summary of studies of childhood stroke, many of which did not include PAS, noted half to two thirds of childhood stroke to demonstrate thrombophilias.[20] Sickle cell disease, a risk factor for later pediatric stroke, is not associated with PAS.

Most studies of risk factors for pediatric stroke other than thrombophilias have chiefly involved older children, and most have been in highly selected samples. One multivariable case-control study in a defined population found risk of PAS to be increased in the presence of a maternal history of infertility (OR 7.5). Other identified factors were oligohydramnios, preeclampsia, prolonged rupture of membranes, cord abnormality, chorioamnionitis, and primiparity.[4] Infertility and chorioamnionitis have been associated in other studies with risk of neonatal encephalopathy and cerebral palsy. Multiple risk factors were associated with markedly higher risk than single factors alone.

It is rare that >1 singleton child in a sibship is affected by PAS, yet much of the research in this disorder has been centered on the genetic thrombophilias, whereas environmental risk factors have been understudied. It is likely to be environmental risk factors, interacting with genetic vulnerabilities, that enable changes of management to prevention of some share of PAS.

Prevention?

PAS affects many individuals and families and often produces lasting disability. It would obviously be highly desirable to prevent some proportion of this disorder. A variety of special challenges would face the testing of interventions for PAS, however. The time of onset of PAS is usually unknown, and many such strokes probably occur, or have the stage set for their occurrence, before birth. Therefore, the patient to be treated might well be the mother, but the outcome to be measured is in the child and is perhaps identifiable only months after the birth. A number of medical specialties, treatment settings, and medical record systems would be involved in a study of prevention of PAS. Although contributing a substantial share of neurological morbidity in children, PAS occurs at a rate of 1 in several thousand term births, presenting a logistic problem in study design. We do not know a constellation of risk factors that could identify prospectively the mother-child pairs at sufficiently high risk to justify interventions that might themselves entail risk. Specific stage-dependent vulnerabilities of the infant could influence outcome in ways difficult to predict. In addition to a general wariness about interventions in the neonate, there would be concerns related to the fact that, in addition to the enzymatic effect in the catalysis of the coagulation cascade, thrombin and the other serine proteases involved in hemostasis have potential effects via protease-activated receptors, and some of these can influence the developing brain.

In view of the many medical, administrative, and ethical concerns that would be aroused by a proposal to test novel interventions for the prevention of PAS, it is likely to be some time before we see such testing. In the meantime, some obvious and safe measures might benefit patients. Women at risk for clotting disorders by virtue of personal or family history of thromboembolic events or known thrombophilias should be counseled about smoking, weight control, use of compression hosiery during lengthy travel or other immobilization, and so on. When pregnant, they should be referred for specialist obstetrical care. Dehydration, a risk factor for thrombosis, is common in labor and is associated with increases in coagulation indices,[21] and therefore careful attention to fluid intake and output during labor is indicated as a harmless and potentially useful intervention. An alerting

system to remind medical caregivers of patients' risk status and encourage simple interventions such as hydration and compression hosiery produced a decrease in thrombotic events in nonpregnant adult inpatients.[22] While we await the hoped-for trials of new interventions to prevent PAS, it may be wise to fall back on the conscientious application of common sense.

Conclusions

PAS has recently been recognized as a not-rare disorder that contributes an important share of lifelong neurological morbidity. Although knowledge has advanced, it is still incomplete. The disorder involves a range of medical specialists, the literature is scattered, and the methodology of many of the studies is suboptimal. The need for further research is clear.

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Disclosures

None.

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