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Epidemiology and classification of perinatal stroke

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SUMMARY

Stroke is an important cause of mortality and chronic morbidity in infants and children. Case definitions for perinatal stroke have varied among studies by clinical and laboratory criteria. A recent US National Institutes of Health workshop on perinatal stroke provided consensus recommendations on the definition and classification of perinatal stroke. The incidence of perinatal stroke has been estimated at 1 in 1600 to 5000 births. The clinical presentation of perinatal stroke depends on the time of diagnosis, acute or delayed, but most will present with seizures. Risk factors for perinatal stroke have not been well studied. Several maternal and neonatal disorders have been reported in infants with perinatal stroke. Children who suffer perinatal stroke typically develop long-term disabilities including motor deficits, cognitive and behavioral disorders, and epilepsy. More than half will develop long-term motor or cognitive problems and the recurrence rate after perinatal stroke is very low.

1. Introduction

Over the last several years, our knowledge of perinatal stroke has substantially improved, but much work remains. Recent epidemiological studies have provided important information on the incidence, risk factors, and outcome of stroke in neonates. Factors associated with stroke in the perinatal period include maternal disorders, blood disorders, cardiac disorders, infection, and other miscellaneous disorders. It is clear that stroke is an important cause of mortality and chronic morbidity in children. Of the infants who suffer a stroke each year, more than half will have permanent motor or cognitive disability. The recurrence rate after perinatal stroke is less than 3% and there are no established treatment or prevention strategies.

This paper discusses the epidemiology of arterial ischemic stroke occurring in the perinatal and neonatal periods, including both cerebrovascular events that are diagnosed during the perinatal period and also those diagnosed retrospectively, when evidence of hemiparesis or postneonatal seizures leads to later evaluation and neuroimaging.

2. Definition and classification

Perinatal stroke typically refers to neurologic signs and symptoms due to a vascular cause around the time of birth, with confirmatory evidence by neuroimaging or pathology. Case definitions for perinatal stroke studies have varied by age at diagnosis and by clinical and laboratory criteria. Perinatal stroke occurs most often in term or near-term infants, but is also reported in preterm infants.[1,2] Diagnostic confirmation of perinatal stroke is typically based on neuroimaging findings, but autopsy criteria have been used in the past.[3] The time at diagnosis is usually within the first few days of life, but some studies have included cases that were identified after the perinatal period. A diagnosis of presumed perinatal stroke is considered when post-perinatal neuroimaging reveals chronic changes suggestive of a stroke during an earlier period. Although the precise timing of this injury cannot be determined, the stroke is presumed to be perinatal in onset if the infant had been neurologically well since birth without any symptoms of acute stroke. It is unclear whether these remotely diagnosed cases should be included, as the underlying risk factors and outcome may differ. Why these strokes are not captured in the perinatal period is unclear, but is likely related to a case-finding strategy that requires clinical events and imaging studies. Some infants with stroke may not manifest symptoms to elicit imaging studies, or the studies that are performed are not sensitive enough to detect acute ischemic stroke. Ultrasound may be less sensitive for the detection of stroke than computed tomography or magnetic resonance imaging (MRI).[4] Diagnostic criteria for stroke may be negative in cases where early imaging studies are normal.[5,6] Studies of perinatal stroke have also differed in the inclusion of stroke subtypes: perinatal arterial ischemic stroke, cerebral sinovenous thrombosis, intracerebral hemorrhage, and periventricular venous infarction.

In August 2006, the United States National Institutes of Health convened a workshop on perinatal stroke to develop consensus

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recommendations on the definition and classification of perinatal stroke. The participants proposed a working definition of perinatal stroke to include 'a vascular event causing focal interruption of blood supply, occurring between 20 weeks of fetal life through 28th postnatal day, and confirmed by neuroimaging or neuropathology studies.' The workshop panel also classified perinatal stroke according to two major subtypes, ischemic (including cerebral venous thrombosis) and hemorrhagic perinatal stroke. [7]

3. Incidence

The incidence of perinatal stroke has been estimated at 1 in 1600 to 5000 births.[8–12] Incidence estimates have been difficult to interpret due to the variability in clinical and diagnostic criteria, number of cases, and underlying population. In most studies, cases were defined as infants with arterial ischemic stroke diagnosed in the neonatal period. More recent studies have included retrospectively diagnosed cases as well as hemorrhagic stroke. A population-based study of perinatal stroke in the USA that included acutely and retrospectively diagnosed cases found an overall incidence of 20 per 100 000 live births.[10] A study in Estonia which included acute, delayed, and hemorrhage cases reported a much higher rate at 63 per 100 000 live births.[12] In both of these studies, retrospectively diagnosed cases were more common than acute cases and suggest that the burden of perinatal stroke may be greater than in previous reports.

4. Clinical presentation

The clinical presentation of perinatal stroke depends on the age at diagnosis. In infants who are diagnosed in the newborn period, most present with seizures. There may also be signs and symptoms of neonatal encephalopathy such as lethargy, hypotonia, feeding difficulties, or apnea. In infants with presumed perinatal stroke who are not diagnosed until months later, the presentation includes focal hand weakness, delayed milestones, and/or seizures. Whether an infant is diagnosed in the newborn period or several months later may depend on the size and location of the stroke and other clinical factors. It seems possible that infants with certain patterns of injury, such as those involving the basal ganglia that spare the cortex, may be more difficult to diagnose in the newborn period because these infants are less likely to exhibit neonatal seizures. In a large series by Golomb of presumed perinatal stroke cases, 40% of the strokes were restricted to small perforating arteries of the middle cerebral artery.[13] A second study of late-diagnosed cases revealed that only 40% had cortical involvement.[12] At present, there are limited data on differences in underlying risk factors among acutely and retrospectively diagnosed cases that could account for time at diagnosis. Maternal and pregnancy-related disorders including chorioamnionitis, placental disorders, and birth asphyxia seem to be more prevalent in acutely diagnosed cases.[10,12] These findings suggest that the presence of specific clinical factors may predispose to seizures or symptoms that lead to a diagnosis of perinatal stroke in the newborn period.

5. Risk factors

Risk factors for perinatal stroke have not been well studied. Most studies of perinatal stroke have been descriptive and have provided little information on quantitative risk estimates, environmental factors, and genetic and environmental interactions. There have been few controlled studies of factors specific to stroke risk in the perinatal period, such as maternal characteristics, placental disorders, and other complications of birth and pregnancy. Environmental factors related to the peripartum period likely play a major role in the perinatal stroke as the recurrence rate is extremely low. Several maternal and neonatal disorders have been reported in infants with perinatal stroke (Table 1).

5.1. Maternal coagulation disorders

Pregnancy is a time of relative hypercoagulability during which several plasma proteins are affected and thrombin generation is increased. Venous thromboembolism is common during pregnancy with risk highest during the third trimester and puerperium,[14] time periods when most perinatal strokes are likely to occur. The addition of a coagulation abnormality in the setting of pregnancy may lead to thrombosis. Maternal coagulation disorders are associated with an increased risk of thrombosis in pregnancy[15] and perinatal stroke. Two recent studies found an increased rate of specific acquired and genetic coagulation abnormalities among mothers of children with perinatal stroke.[16,17] In the first study, prothrombotic abnormalities were identified in 55% of mothers and 50% of infants with perinatal stroke.[16] A second case–control study from Israel revealed similar findings with 68% of mothers and 64% of infants with a coagulation abnormality. In addition, this study found that the presence of factor V Leiden (FVL) or antiphospholipid

Table 1
Maternal and infant disorders reported with perinatal stroke.

Maternal disorders
Infertility
Pre-eclampsia
Chorioamnionitis
Autoimmune disorders
Coagulation disorders
Twin to twin transfusion syndrome
Cocaine use
Placental disorders
Placental thrombosis
Placental abruption
Placental infection
Fetomaternal hemorrhage
Placental chorioangioma
Blood, homocysteine and lipid disorders
Polycythemia
Disseminated intravascular coagulopathy
Factor V Leiden mutation
Protein S deficiency
Protein C deficiency
Prothrombin 20210A mutation
Homocysteine
Elevated Lipoprotein a
Factor VIII
Antiphospholipid antibodies
Cardiac disorders
Congenital heart disease
Patent ductus arteriosus
Pulmonary valve atresia
Cardiac surgery
Infectious disorders
Meningitis
Systemic infection
Miscellaneous disorders
Vascular maldevelopment
Arterial dissection
Trauma
Catheterization
Dehydration
Extracorporeal membrane oxygenation (ECMO)