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Topical Review

Perinatal Arterial Ischemic Stroke: Presentation, Risk Factors, Evaluation, and Outcome

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ABSTRACT

BACKGROUND: Perinatal arterial ischemic stroke is as common as large vessel arterial ischemic stroke in adults and leads to significant morbidity. Perinatal arterial ischemic stroke is the most common identifiable cause of cerebral palsy and can lead to cognitive and behavioral difficulties that are amortized over a lifetime. **METHODS:** The literature on perinatal arterial ischemic stroke was reviewed and analyzed. **RESULTS:** Risk factors for perinatal arterial ischemic stroke include those that are maternal, neonatal, and placental. The most common clinical signs at presentation are seizures and hemiparesis. Evaluation should begin with thorough history acquisition and physical examination followed by magnetic resonance imaging of the brain, with consideration of magnetic resonance angiography of the head and neck, echocardiogram, and thrombophilia evaluation. Treatment beginning early to include physical, speech, and occupational therapies including constraint-induced movement therapy and close cognitive and developmental follow-up may be beneficial. Future treatments may include transcranial magnetic stimulation, hypothermia, and erythropoietin. **CONCLUSIONS:** Perinatal arterial ischemic stroke comprises a group of arterial ischemic injuries that can occur in the prenatal, perinatal, and postnatal periods in term and preterm infants with different types of perinatal arterial ischemic stroke having different clinical presentations, risk factors, and long-term outcomes.

Keywords: neonatal, perinatal, presumed perinatal, ischemic, stroke

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Introduction

Neonatal stroke remains incompletely understood. Similar to stroke in older children and adults, neonatal stroke may be either hemorrhagic or ischemic; however, the presentation and etiologies of stroke in neonates differ from those of both older age groups and, in many cases, remain unrecognized. A workshop convened by the National Institutes of Health addressed ischemic perinatal stroke. Ischemic perinatal stroke was defined as "a group of heterogeneous conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through twenty-eighth postnatal day confirmed by neuroimaging or neuropathologic studies."[1] Thus, the clinical entity of ischemic perinatal stroke includes focal or multifocal ischemic injury to the central nervous system of either arterial or venous etiology that can occur during the prenatal, intrapartum, or postnatal period. This review focuses specifically on arterial ischemic stroke (AIS) in the neonate that investigators have consistently defined as a pattern of ischemic brain injury in an arterial distribution.[2-4]

AIS during childhood occurs most frequently in the perinatal period. The incidence of AIS in the neonate is similar to the incidence of large artery AIS in adults and is 17 times greater than the incidence of AIS in children.[5] In term neonates, AIS is the most common recognized cause of cerebral palsy and is the second most common underlying etiology of neonatal seizures.[6,7]

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First, we will discuss the classification and the epidemiology of perinatal AIS. Next, we will describe the known maternal, placental, and neonatal risk factors associated with perinatal AIS. Then, we will review the common clinical presentations and imaging findings and discuss the recommended evaluation and treatment. We will conclude with a discussion of outcome after perinatal AIS.

Classification

As mentioned previously, perinatal AIS refers to a distinct pattern of ischemic brain injury in an arterial distribution that occurs during the prenatal, intrapartum, or neonatal period. Perinatal AIS can be subclassified according to the time of diagnosis as fetal, neonatal, or presumed perinatal AIS. Fetal AIS is diagnosed before birth through the use of fetal imaging methods or in stillbirth on the basis of neuropathologic examination that reveals a pattern of ischemic brain injury in an arterial distribution. Neonatal AIS constitutes an acute presentation of encephalopathy manifesting as seizure, altered mental status, and/or neurological deficit between birth and the twenty-ninth postnatal day for which a pattern of ischemic brain injury in an arterial distribution is evident by clinical neuroimaging. Presumed perinatal AIS is diagnosed in individuals >28 days of age with focal neurological deficits and a corresponding chronic infarct in arterial distribution in whom it is presumed (but not proven) that the ischemic injury occurred between the twentieth week of fetal life through the twenty-eighth postnatal day but was not detected during that period.[1-4] Neonatal AIS can be further categorized as a term or preterm clinical event depending on the gestational age of the infant. Preterm neonatal AIS is defined as an AIS occurring in a preterm infant variably defined by investigators as less than 35 weeks to 37 weeks of gestational age.[5,8,9]

Epidemiology

The incidence of neonatal AIS in term infants has been reported to reside between one in 2300 and one in 5000 live births.[7,10,11,12] AIS occurs even more frequently among preterm newborns. Benders et al.[9] found that preterm AIS occurred at a rate of seven per 1000 infants born at or before 34 weeks of gestation. A male predominance occurs in term neonatal AIS but has not been observed in preterm neonatal AIS.[2-4,12] Studies on the incidence of presumed perinatal stroke are scarce. One study, which combined hemorrhagic and ischemic presentations of presumed perinatal stroke found an incidence of one in 2307 live births with a female predominance.[11]

Risk factors

Risk factors for perinatal AIS comprise maternal, neonatal, and placental conditions (Table 1). Maternal risk factors include infertility, preeclampsia, prolonged rupture of membranes, maternal smoking, intrauterine growth retardation, maternal fever, thrombophilia, and chorioamnionitis.[5,13-16] The risk of neonatal AIS increases as the number of the pregnant mother's risk factors rises.[5] Many different studies have demonstrated different maternal risk factors to be independently associated with neonatal AIS. One study using multivariate analysis demonstrated that neonatal AIS in the term infant was associated with maternal fever during delivery.[13] Another study determined that maternal smoking was the only maternal risk factor associated with neonatal AIS.[14] In the International Pediatric Stroke Study (IPSS) cohort, maternal risk factors were uncommon except gestational hypertension and/or preeclampsia, which occurred in 10% of mothers.[17]

TABLE 1.
Risk Factors for Perinatal Arterial Ischemic Stroke

Type of Risk Factor	Risk Factor
Maternal	Thrombophilia
	Infertility
	Prolonged rupture of membranes
	Preeclampsia
	Smoking
	Intrauterine growth retardation
	Infection
	Maternal fever
Fetal	Thrombophilia
	Congenital heart disease
	Arteriopathy
	Hypoglycemia
	Perinatal asphyxia
	Infection
	Need of resuscitation
	Apgar score of <7 at 5 minutes
Placental	Chorioamnionitis
	Placental infarcts
	Placenta weighing less than tenth percentile

Fewer studies exist that examine maternal risk factors in preterm infants with neonatal AIS. Golomb et al. examined infants with preterm neonatal AIS and found that 30% of the mothers had a history of maternal infection, 22% had a history of gestational bleeding, 17% had a history of maternal smoking, and 9% had a history of maternal drug use.[2] Benders et al.,[9] on the other hand, was not able to demonstrate any relationship between preterm neonatal AIS and any known maternal risk factor.

Even fewer studies have examined maternal risk factors in presumed perinatal AIS. Golomb et al.[18] found that most of the children diagnosed with presumed perinatal AIS had maternal histories of preeclampsia, maternal infection, bleeding during pregnancy, or gestational diabetes. Moreover, in a study examining maternal-infant pairs including infants with either presumed perinatal or neonatal AIS, 78% of the dyads possessed at least one thrombophilia risk factor. In this cohort, factor V Leiden heterozygosity, protein C deficiency, and antiphospholipid antibodies carried significant risk of stroke compared with controls.[16]

Neonatal risk factors include congenital heart disease (CHD), prothrombotic abnormalities, 5-minute Apgar score of <7, hypoglycemia, and infection.[11,13,16,19-22] Mechanical force applied to the newborn's head and neck during labor may also lead to injury of craniocervical arteries increasing risk of arterial dissection and stroke.[23] A recent study using multivariate analysis determined that hypoglycemia, an Apgar score of <7 at 5 minutes, and