Placental Pathology in Neonatal Stroke: A Retrospective Case-Control Study

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Objective To assess the association of placental abnormalities with neonatal stroke.

Study design This retrospective case-control study at 3 academic medical centers examined placental specimens for 46 children with neonatal arterial or venous ischemic stroke and 99 control children without stroke, using a standard protocol. Between-group comparisons used χ^2 and Fisher exact *t* test. Correlations used Spearman correlation coefficient.

Results Case placentas were more likely than controls to meet criteria for ≥1 of 5 major categories of pathologic abnormality (89% vs 62%; OR, 5.1; 95% CI, 1.9-14.0; $P = .0007$) and for ≥2 categories (38% vs 8%; OR, 7.3; 95% CI, 2.9-19.0; $P < .0001$). Fetal vascular malperfusion occurred in 50% of cases and 17% of controls (OR, 4.8; 95% CI, 2.2-10.5; $P = .0001$). Amniotic fluid inflammation occurred in 46% of cases with arterial ischemic stroke vs 25% of controls (OR, 2.6; 95% CI, 1.1-6.1; $P = .037$). There was evidence of a "stress response" (meconium plus elevated nucleated red blood cells) in 24% of cases compared with 1% of controls (OR, 31; 95% CI, 3.8-247.0; $P < .0001$).

Conclusions Placental abnormality was more common in children with neonatal stroke compared with controls. All placental findings represent subacute-to-chronic intrauterine stressors. Placental thrombotic processes were associated with both arterial and venous stroke. Our findings provide evidence for specific mechanisms that may predispose to acute perinatal stroke. Amniotic fluid inflammation associated with neonatal arterial ischemic stroke deserves further investigation. *(J Pediatr 2017;■■:■■-■■).*

Neonatal ischemic stroke is defined as a focal or multifocal infarction in an arterial or venous distribution that occurs between 20 weeks' gestation and the 28th postnatal day.[1] It affects between 1 in 1600 and 1 in 5000 term newborns, with significant and lasting neurologic morbidity.[2,3] Advances in neuroimaging, primarily magnetic resonance imaging (MRI), have permitted identification and classification of newborn stroke into arterial or venous etiologies as well as later characterization of presumed perinatal events.[1] Although perinatal stroke has been associated with a number of risk factors, a single, unifying etiology has not been identified.[1,4,5]

Speculation that stroke in the newborn represents interactions among infant, maternal, and placental processes has existed for some time. Attention to placental factors in neonatal brain injury has focused on neonatal encephalopathy, perinatal hypoxic-ischemic brain injury, and cerebral palsy beyond the neonatal period.[6-19] However, these studies lack sufficient numbers of infants with hemiplegic cerebral palsy or imaging-confirmed stroke to elucidate the placental factors associated with neonatal stroke. Nevertheless, 2 relevant major themes have emerged from this work: the association of neonatal neurologic injury with thrombosis or other abnormality of fetal placental vasculature, and with intrauterine infection or inflammation.

The study of placental factors related to neonatal arterial or venous stroke has been limited to small case series with scant data about both infant and placenta. In infants with imaging-confirmed stroke whose placentas were examined, a substantial proportion of examined placentas have shown abnormalities consistent with thrombosis and/or inflammation, but the mechanistic significance of these abnormalities and their prevalence compared with controls remains unclear.[2,11,20-31]

Thromboemboli have been hypothesized to arise in the fetal circulation of the placenta and travel through the umbilical vein to cross either the patent foramen ovale or patent ductus arteriosus to become arterial systemic thromboemboli, some of which occlude cerebral vasculature.[3,30,32] Exploration of fetal thrombotic vasculopathy in neonatal stroke has included study of thrombophilia in these children. Recent data show no increase in thrombophilia in perinatal stroke cases compared with controls[33] and no connection between thrombophilia and recurrent

AIS	Arterial ischemic stroke
IUGR	Intrauterine growth restriction
MRI	Magnetic resonance imaging

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The authors declare no conflicts of interest.

Portions of this study were presented at the American Academy of Neurology Annual Meeting, April, 2016, Vancouver, British Columbia, Canada and the International Stroke Conference, February 2015, Nashville, Tennessee.

https://doi.org10.1016/j.jpeds.2017.11.061

stroke.[34] Finally, stroke rarely recurs in children with neonatal stroke,[5,35] arguing against fetal thrombophilia as a primary cause of perinatal stroke.

The maternal and fetal membranes may also be exposed to infection or other causes of inflammation, triggering inflammatory cascades recognized as risk factors for hypercoagulability and stroke.[27,36-38] We sought to characterize in detail the clinical history and placental pathology of mother–infant–placenta triads affected by neonatal stroke and controls to understand better the possible risk factors and mechanisms. We hypothesized that placental abnormality would be more prevalent in cases than in controls. Additionally, we investigated whether a specific placental pathology would be associated with a specific neonatal stroke type.

Methods

We retrospectively reviewed cases of neonatal and presumed perinatal ischemic stroke referred to our program from January 2005 to January 2015. Patients with neonatal stroke were identified by referral for neurology consultation from 3 neonatal intensive care units (Boston Children's Hospital, Beth Israel Deaconess Medical Center, and Brigham and Women's Hospital), comprising approximately 125 neonatal beds. Neonatal arterial ischemic stroke (AIS) or venous stroke was defined as acute, focal, or multifocal cerebral infarction in either arterial or venous distribution occurring between 20 weeks' gestation and 28 days after birth.[1] Presumed perinatal AIS was defined as imaging evidence of focal or multifocal infarction in an arterial territory without clinical evidence of recent stroke.[1] Owing to the small number of presumed perinatal AIS cases, the 2 subgroups were analyzed together.

All patients presenting in the neonatal period underwent MRI using a standard neonatal protocol within several days of symptom onset or after abnormal ultrasound examination of the head; patients presenting later in infancy or childhood underwent computed tomography or MRI using standard protocols at the time of clinical presentation. Images were reviewed by a single pediatric neuroradiologist to diagnose stroke, and to determine stroke type and location. All included cases had evidence of acute or remote focal infarction consistent with a single arterial or venous territory, or multifocal infarction consistent with arterial embolism (**Figure 1**). Cases with watershed or patchy symmetric distribution infarction were excluded, because these features were more consistent with diffuse hypoxic-ischemic injury.

Medical records from the consulting hospital, and the delivery hospital if different, were reviewed for information including prenatal history, complications of labor and delivery, family history suggestive of thrombophilia, clinical presentation, and laboratory evaluation of mothers and infants. Most children continued to be followed at our center and, therefore, record review included those from outpatient clinical follow-up, including any additional or repeat laboratory evaluation. Thrombophilia testing performed varied over the time of the study. All cases had family history of thrombophilia assessed as routine practice. The definition of a positive thrombophilia evaluation has been previously described and appears in **Table I** (available at www.jpeds.com).[34] Clinical and laboratory data were abstracted by a single pediatric neurologist with additional laboratory review by a pediatric hematologist.

Placental specimens prepared as hematoxylin and eosin–stained slides were obtained from the delivery hospitals and examined by a single pathologist, blinded to individual patients' clinical data and specific stroke type. Placental pathologic findings were recorded and tabulated for 5 predefined major categories of placental abnormality using established protocols (**Figures 2** and **3** [both available at www.jpeds.com])).[40] The pathologic category of maternal vascular malperfusion was assigned when ≥3 of the following diagnostic features were present: small placenta, narrow cord diameter, placental infarction, abruption, distal villous hypoplasia, excess cytotrophoblast fibrinoid islands, excessive calcification, aggregated terminal villi, increased syncytial knots, decidual arteriopathy, increased perivillous fibrin, or chorangiosis (when associated with other findings in this category).[40] The pathologic category of fetal vascular malperfusion was assigned when ≥2 of the following diagnostic features were present: avascular villi, villous stromal karyorrhexis, delayed villous maturation, marked chorionic plate or stem villous vessel dilation, chorionic or stem villous thrombosis, nuchal cord, true knot, marginal cord insertion, body cord, or oligohydramnios.[40] Amniotic fluid inflammation was indicated on the maternal side by acute chorioamnionitis or subchorionitis and on the fetal side by umbilical cord vasculitis and/or chorionic plate vasculitis. The overall category of extensive noninfectious chronic villitis was noted and was classified as high grade or low grade.[40] Finally, we classified large placenta in association with chorangiosis.[40] Other abnormalities noted in this placental cohort included chorion nodosum, villous edema, diffuse chorioamnionic hemosiderosis, and meconium umbilical vascular necrosis. Additionally, the presence of meconium-laden macrophages within the membranes or chorionic plate was noted, and nucleated red blood cells were quantified.

When ≥20 nucleated red blood cells were seen for every 100 white blood cells and meconium-laden macrophages were also present, we termed this the "stress response."[41,42]

Controls were selected from infants born at a participating institution that served as the delivery hospital for one-half of the case infants, in the same period (2005-2015). These were infants whose placentas had previously been submitted for clinical pathologic review and examined by the same pathologist using the same standard practice as for the cases. From this sample ≥2 controls were randomly selected such that they were 2:1 matched to cases by gestational age and year of delivery. Indications for placental review were collected. After matching, clinical records for control infants were reviewed by a pediatric neurologist for any complications in the newborn period prompting triage in or admission to the neonatal intensive care unit and for any imaging, consultation, or discharge documentation indicating neurologic concerns including diagnosis of stroke or seizure. No concerns for permanent neurologic injury were identified for any control infant.

FLA 5.5.0 DTD ■ YMPD9634_proof ■ January 31, 2018