Placental Pathology in Neonatal Stroke
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Placental Pathology in Neonatal Stroke

WHAT’S KNOWN ON THIS SUBJECT: Neonatal stroke is recognized as a cause of infant morbidity and neurodevelopmental disability. The placenta has become an organ of interest as a contributor to cerebral palsy and neurologic disability; however, placental pathology has not been systematically described in stroke.

WHAT THIS STUDY ADDS: This study reviews placental pathology in patients presenting with neonatal stroke near delivery and correlates this with clinical presentation, outcome, and risk factors. We suggest that multiple risk factors are involved in neonatal stroke, and placental pathology may be a contributor.

abstract

OBJECTIVE: Neonatal stroke is increasingly recognized, and risk factors have been identified. The placenta has been implicated as a potential contributor to neonatal stroke; however, pathology has not been previously described. This case series systematically evaluates prenatal, maternal, and neonatal risk factors and describes placental pathology in 12 cases of neonatal stroke.

PATIENTS AND METHODS: We reviewed the Canadian Pediatric Ischemic Stroke Registry from 1992 to 2006, which consists of 186 neonatal stroke patients. Twelve patients with symptomatic cerebral arterial ischemic stroke or sinovenous thrombosis had their placenta available for pathologic examination. Clinical presentation; maternal, prenatal, and neonatal risk factors for stroke; and patient outcome were collected retrospectively from patient charts. Gross and microscopic placental pathology was described and classified into 4 pathologic categories.

RESULTS: Of 12 patients studied, 10 patients were male, 5 patients had arterial ischemic stroke, and 7 patients had sinovenous thrombosis. Maternal risk factors were identified in 5 cases, prenatal risk factors in 10 cases, and neonatal risk factors in 10 cases. Placental lesions were present in 10 cases and were classified as thromboinflammatory process in 6 cases, sudden catastrophic event in 5 cases, decreased placental reserve in 3 cases, and stressful intrauterine environment in 2 cases.

CONCLUSIONS: This study reviews detailed placental pathology in a selected cohort of patients presenting near the time of delivery and correlates this with clinical presentation, outcome, and risk factors for neonatal stroke. Our results suggest that multiple risk factors are involved in neonatal stroke, and placental pathology may be a contributing factor. The implications of specific placental lesions remain to be determined with larger, case-controlled studies. Pediatrics 2011;127: e722–e729
Neonatal stroke is increasingly recognized as a significant cause of infant morbidity and neurodevelopmental disability. With an estimated incidence of 1 in 2500 live births, the perinatal period confers the highest risk for ischemic stroke in patients under 18 years of age. With increased recognition, risk factors for neonatal stroke recently have been identified. These risk factors include maternal conditions such as prothrombotic disorders, infertility, and preeclampsia; prenatal factors such as fetal heart rate abnormalities, intrauterine growth restriction, chorio-amnionitis, and prolonged rupture of membranes; and neonatal factors including infection, prothrombotic states, and congenital heart disease. Studies suggest that multiple risk factors may be implicated in neonatal stroke. The placenta recently has become an organ of interest in the search for causes of cerebral palsy and other neurologic disabilities. The placenta provides the sole blood supply for the fetus via an elaborate network of blood vessels within chorionic villi that penetrate the maternal endometrium. These chorionic villi are bathed in maternal blood through surrounding sinusoidal spaces. The role of the placenta in neonatal brain injury has been discussed by Redline and O’Riordan who described typical patterns of placental lesions found in children with cerebral palsy. One study describing placental lesions in a group of term infants with adverse neurologic outcomes from a medicolegal registry showed a significantly higher prevalence of chronic villous degenerative changes, chorioamnionitis with severe fetal inflammatory response, and pathologic umbilical cord abnormalities in case subjects compared with healthy control subjects. Overall, 66% of the medicolegal registry cases had 1 or more significant placental lesions compared with 18% in the comparison group. In another large case-controlled study of patients presenting with neonatal encephalopathy, placental lesions of infection, thrombosis, and disturbed uteropelvic flow were significant independent factors in the neonatal encephalopathy group.

Neonatal stroke is a recognized cause of hemiplegic cerebral palsy. In contrast to more diffuse perinatal brain insults underlying cerebral palsy, stroke is attributed to large-vessel obstruction and is typically a focal injury within an otherwise intact brain. Many authors suggest the placenta as an additional risk factor for neonatal stroke. Although some studies investigating the incidence of thrombi in the neonate have established pathologic findings in the placenta, no study has systematically analyzed the placenta in neonates with stroke. This study aimed to describe placental pathology in neonates diagnosed with either arterial ischemic stroke (AIS) or cerebral sinovenous thrombosis (CSVT). In addition, previously described risk factors for neonatal stroke were identified to provide a perspective on other factors that may be implicated in, or contribute to, the pathophysiology of neonatal stroke.

**PATIENTS AND METHODS**

**Case Ascertainment**

Patients were identified in the Canadian Pediatric Ischemic Stroke Registry—Toronto site, part of a prospective database containing information on pediatric stroke patients across the country. All patients from the Toronto site diagnosed from January 1992 to December 2006 were reviewed, and those with a diagnosis of neonatal stroke (defined as stroke diagnosed within the first 28 days of life) and born term (>37 weeks' gestational age) or preterm (34–37 weeks' gestational age) were included if their placenta was available for review. Regional birthing centers typically only retain placentas at the time of delivery for newborns with perinatal complications.

**Patient Characteristics**

Patient records were retrospectively reviewed to collect patient characteristics, mode of diagnosis, and distribution of cerebral infarcts according to vascular territory(ies). Recognized maternal, prenatal, and postnatal risk factors for perinatal stroke were identified. Neuroimaging was completed according to clinical diagnostic standards. Computed tomography was completed acutely in the majority of cases, with magnetic resonance imaging when available. Magnetic resonance imaging sequences included T1, T2, fluid-attenuated inversion recovery, diffusion weighted, apparent diffusion coefficient, and gadolinium.

**Placental Analysis**

Placentas were reviewed by a single observer, a perinatal anatomic pathologist (Dr Sandra Viero), according to a standardized technique. Gross examination was performed after fixation in 10% formalin. Cord abnormalities were described, and 2 sections of cord, 1 including the placental insertion site, were sampled. An extraplacental membrane roll including decidua was sampled. The trimmed disk weight was recorded. The placental disk was sectioned at 1-cm intervals with at least 2 random sections sampled and any lesions sampled. Sections were submitted for routine processing, paraffin embedding, and staining with hematoxylin and eosin. Gross and histologic characteristics were noted and additionally classified according to subcategories established by Redline. Placental lesions were pathologically categorized as (1)
a sudden catastrophic event, (2) a thrombo-inflammatory process, (3) a decreased placental reserve, or (4) an adaptive response to stressful intrauterine environment. The placental lesions observed in patients categorized under “sudden catastrophic event” include retroplacental hematoma and acute umbilical cord occlusion, such as by thrombosis, true cord knots, cord overcoiling, or abnormal cord insertion sites. For the thrombo-inflammatory processes, placental lesions included acute chorioamnionitis, chronic villitis, choriionic vessel thrombi, stem vessel thrombi, and the presence of avascular fibrotic villi. Decreased placental reserve was defined by 2 or more of the following: multiple placental infarcts; distal villous immaturity; and placental weight less than the 10th percentile for gestational age.32 The final category, indicating adaptive responses as a result of a stressful intrauterine environment, required increased fetal nucleated red blood cells or an increase in the number of fetal capillaries per villous cross-section, termed villous chorangiosis.

**Patient Outcome**

Patient outcomes at 2 years were collected. Outcomes were categorized as normal, mild motor dysfunction (fine motor problems, mild developmental delay), significant motor dysfunction (hemiparesis), language delay, and presence of seizure disorder.

**RESULTS**

**Patient Characteristics**

The Stroke Registry consisted of 186 patients with neonatal stroke at the Hospital for Sick Children between 1992 and 2006. Of those patients, 12 had placentas available for pathologic examination by our pathologist. Of the 12 patients studied, 10 were male and 5 were diagnosed with AIS and 7 with CSVT. All were singleton births, with 11 infants born at term (≥38 weeks) and 1 late preterm infant born at 34 weeks’ gestation. Birth weights ranged from 1.6 kg to 4.17 kg, with a median of 3.41 kg. One-minute Apgar scores ranged from 1 to 10, with a median of 4.5, and 5-minute Apgar scores ranged from 2 to 10, with a median of 6.

**Clinical Data**

Ten patients (83%) presented on the first day of life with signs of neonatal encephalopathy. Other presenting signs can be found in Table 1. There was no difference in clinical presentation between the patients with AIS versus CSVT. No patients with AIS were treated with antithrombotic therapy, whereas 3 patients with CSVT received antithrombotic therapy.

Risk factors for neonatal stroke are shown in Table 2. Maternal risk factors were identified in 5 of 12 cases (42%). No patients had preeclampsia or diabetes; maternal thrombophilias were not routinely tested. Prenatal risk factors for neonatal stroke were identified in 10 of 12 cases (83%). Neonatal risk factors for neonatal stroke were present in 10 of 12 cases (83%). Four patients had congenital heart disease with a right-to-left shunt, 1 was postoperative day 1 from a cardiac procedure at the time of presentation. Follow-up on coagulation profiles of our study patients did not reveal any significant prothrombotic disorders.

**Neuroimaging**

The diagnosis of AIS was made within a median of 4 days (range: 1–5 days) and CSVT within a median of 2 days (range: from 1–8 days), according to neuroimaging findings. Ischemic changes were consistent with an arterial or venous distribution, rather than diffuse hypoxic injury often seen in hypoxic ischemic encephalopathy. The distribution of infarction in patients with AIS was multifocal, involving middle, anterior, and posterior cerebral artery territories in 4 patients (80%) and a single lesion in the left-middle cerebral artery territory in 1 patient. Magnetic resonance angiography was completed acutely (within 3 days of life) in 2 patients, both of which were normal. Two patients developed hemorrhage within the area of infarcts (40%).

Of 7 patients with CSVT, thrombus was seen in the transverse sinuses in 5 patients, superior sagittal sinus in 3 patients, torcular in 3 patients, internal jugular vein in 1 patient, and internal venous system in 1 patient. Six of 7 patients developed parenchymal hemorrhage (86%).

**Placental Analysis**

Placental pathology was evident in 10 of 12 patients (83%), whereas 2 placentas were within normal limits (Table 3). Placental weights ranged from 204 to 808 g, with a median of 487.5 g. Histopathology showed sudden catastrophic event in 5 patients (42%), thrombo-inflammatory process in 6 patients (50%), decreased placental reserve in 3 patients (25%), and stressful intrauterine environment in 2 patients (15%). Mixed placental lesions were found in 5 patients (42%). Two patients had histologic evidence of acute chorioamnionitis (Fig 1), 1 had histologic evidence of moderate chorioamnionitis, and the other had evidence of severe chorioamnionitis, displaying a fetal inflammatory response (funisitis), and 5 patients had placental fetal vessel (Fig 2) or umbilical cord thrombi. Four patients had placental infarcts.

**Patient Outcome**

Of 12 patients in our study, 2 were lost to follow-up. At the 2-year follow-up, 2 patients (both with CSVT) were neurologically normal, 6 patients (4 had AIS and 2 had CSVT) had mild motor dys-
function, and 5 patients (4 had CSVT and 1 had AIS) had language delay. No patients had severe hemiparesis or other significant motor dysfunction, and none had a seizure disorder.

**DISCUSSION**

This is the first study to systematically analyze placental pathology in addition to identifying other potential risk factors in a cohort of patients with symptomatic neonatal AIS and CSVT. Placental lesions identified in 10 of 12 (83%) of our patients with neonatal stroke demonstrate multiple pathologies, in-

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**TABLE 1 Clinical Features of Neonates With AIS and CSVT**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Apgar Score, 1 Min, 5 Min</th>
<th>(Age) Clinical presentation</th>
<th>Diagnosis</th>
<th>(Age) Imaging Modality: Findings (Vascular Territory)</th>
<th>Outcome At 2-Year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2, 3</td>
<td>(Days of life: 1) hypotensive, decreased spontaneous movements</td>
<td>AIS</td>
<td>(Days of life: 4) MRI: multifocal, bilateral infarcts with diffusion restriction (MCA, PCA); (Days of life: 5) CT: single infarct (left MCA); (Days of life: 6) MRI: multifocal, unilateral infarcts with restricted diffusion (left MCA and left ACA); (Days of life: 7) MRA or MRV: normal</td>
<td>Mild motor dysfunction</td>
</tr>
<tr>
<td>2</td>
<td>5, 7</td>
<td>(Days of life: 1) focal seizures, apnea, neonatal encephalopathy</td>
<td>AIS</td>
<td>(Days of life: 1) CT: single infarct (left MCA); (Days of life: 5) CT: single infarct without diffusion restriction (left MCA); (Days of life: 15) MRI: small left MCA branches</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>3</td>
<td>4, 6</td>
<td>(Days of life: 1) focal seizures; hypotension; decreased movements, right side; neonatal encephalopathy</td>
<td>AIS</td>
<td>(Days of life: 5) CT: multifocal bilateral infarcts (left MCA, right MCA, left ACA) Petechial hemorrhage within infarcts; (mo of life: 13) MRI: multifocal bilateral infarcts without diffusion restriction (left MCA, right MCA, left ACA); (mo of life: 13) MRA: attenuated (left MCA)</td>
<td>Mild motor dysfunction</td>
</tr>
<tr>
<td>4</td>
<td>6, 6</td>
<td>(Days of life: 1) focal seizures, hypotension; decreased movements, right side; neonatal encephalopathy</td>
<td>AIS</td>
<td>(Days of life: 2) CT: left subdural hemorrhage plus single infarct (left MCA); (Days of life: 6) MRA: multifocal, bilateral infarcts with restricted diffusion (left MCA, right PCA); petechial hemorrhage within infarcts; (Days of life: 3) MRA: normal</td>
<td>Mild motor dysfunction, language delay</td>
</tr>
<tr>
<td>5</td>
<td>6, 9</td>
<td>(Days of life: 1) focal seizures, apnea, neonatal encephalopathy</td>
<td>AIS</td>
<td>(Days of life: 1) CT: hypotension, neonatal encephalopathy</td>
<td>Mild motor dysfunction, language delay</td>
</tr>
<tr>
<td>6</td>
<td>1, 4</td>
<td>(Days of life: 1) focal seizures, apnea, hypotension, neonatal encephalopathy</td>
<td>CSVT</td>
<td>(Days of life: 1) CT: diffuse edema, (Days of life: 3) MRI: thrombosis in superior sagittal sinus, torcula, bilateral transverse sinuses, no diffusion restriction, punctate hemorrhages bilateral basal ganglia</td>
<td>Language delay</td>
</tr>
<tr>
<td>7</td>
<td>2, 6</td>
<td>(Days of life: 1) hypotension, neonatal encephalopathy</td>
<td>CSVT</td>
<td>(Days of life: 4) MRI: thrombosis in left transverse sinus, left sigmoid, and left internal jugular vein, restricted diffusion bilateral internal capsule, punctate hemorrhages bilateral basal ganglia</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>2, 2</td>
<td>(Days of life: 1) hypotension, neonatal encephalopathy</td>
<td>CSVT</td>
<td>(Days of life: 6) MRI: right transverse sinus with multifocal areas of diffusion restriction, subcortical petechial hemorrhage, (Days of life: 6) CT: thrombosis in bilateral transverse sinuses, torcula</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>9</td>
<td>8, 9</td>
<td>(Days of life: 1) focal seizures, apnea</td>
<td>CSVT</td>
<td>(Days of life: 1) CT, Superior sagittal sinus thrombosis plus hydrocephalus; (Days of life: 2) MRI: thrombosis in superior sagittal sinus</td>
<td>Mild motor dysfunction, language delay</td>
</tr>
<tr>
<td>10</td>
<td>7, 9</td>
<td>(Days of life: 2) focal seizures, apnea</td>
<td>CSVT</td>
<td>(Days of life: 8) CTV: thrombosis in right transverse sinus, (Days of life: 20) MRI: remote left parietal hemorrhagic venous infarct</td>
<td>Language delay</td>
</tr>
<tr>
<td>11</td>
<td>10, 10</td>
<td>(Days of life: 6) focal seizures</td>
<td>CSVT</td>
<td>(Days of life: 7) CT: Thrombi in vein of Galen and internal cerebral veins bilateral frontal lobe hemorrhage, (Days of life: 8) MRI: thrombi in vein of Galen, internal cerebral veins, torcula, and inferior sagittal sinus</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>3, 4</td>
<td>(Days of life: 1) focal seizures, decreased spontaneous movement, neonatal encephalopathy</td>
<td>CSVT</td>
<td>(Days of life: 2) CT: diffuse cerebral edema, thrombus in superior sagittal sinus, hemorrhage right centrum semiovale, (Days of life: 3) MRI/MRV: thrombus in torcula and left transverse sinus, multifocal, bilateral areas of diffusion restriction</td>
<td>Mild motor dysfunction, language delay</td>
</tr>
</tbody>
</table>

MRI indicates magnetic resonance imaging; MCA, middle cerebral artery; PCA, posterior cerebral artery; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; CT, computerized tomography; ACA, anterior cerebral artery.
including decreased placental reserve, thromboinflammatory processes, and sudden catastrophic events. Each of these lesion types may contribute to neonatal stroke by either sending emboli directly into the fetal circulation or by causing an inflammatory process, leading to the formation of a thromboinflammatory process and thus promoting diffuse thrombus formation.

The majority of our patients also had prenatal and neonatal risk factors for neonatal stroke, and it was difficult to determine a predominant cause. Our findings suggest that both AIS and CSVT in the newborn are multifactorial, with a combination of predisposing and triggering factors. This is consistent with previous studies.9,15,19,20 In one case-control study,9 the presence of 3 or more risk factors was associated with a 25-fold increased risk of perinatal stroke compared with those without risk factors.

In our study, 6 patients (50%) presented with placental lesions consistent with fetal thrombotic vasculopathy. Fetal thrombotic vasculopathy is a term proposed by Redline16 to describe ischemic changes in various organs in the newborn.17,18 Histologically, it is defined by clusters containing at least 5 avascular villi (Fig 3) and thrombi in stem vessels or other major placental vessels.19 In a study of 64 perinatal autopsies, 6 cases of fetal thrombotic vasculopathy were present. In patients of 16 patients with fetal thrombotic vasculopathy, a thromboinflammatory process has been associated with thromboemboli in various organs in the newborn.20

TABLE 2: Risk Factors Identified in Neonates With AIS and CSVT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Gestational Age</th>
<th>Placental Weight</th>
<th>Maternal Risk Factors</th>
<th>Prenatal Risk Factors</th>
<th>Neonatal Risk Factors</th>
<th>Placental Risk Factors</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>40 ± 3 wk</td>
<td>204 g (&lt;10th percentile)</td>
<td>None</td>
<td>IUGR, nuchal cord, oligohydrammos</td>
<td>Polycythemia, congenital heart disease</td>
<td>Decreased placental reserve</td>
<td>AIS</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>38 wk</td>
<td>475 g (50th percentile)</td>
<td>None</td>
<td>IUGR, ER C/S</td>
<td>Anemia, congenital heart disease</td>
<td>Thromboinflammatory process</td>
<td>AIS</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>39 wk</td>
<td>600 g (90th percentile)</td>
<td>Primiparity, GBS positive (treated)</td>
<td>FHR abnormalities, ER C/S, fetal-maternal hemorrhage</td>
<td>Anemia</td>
<td>Thromboinflammatory process</td>
<td>AIS</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>36 wk</td>
<td>413 g (25th percentile)</td>
<td>Primiparity</td>
<td>FHR abnormalities, ER C/S</td>
<td>Anemia, systemic thromboses, congenital heart disease, Anemia</td>
<td>Sudden catastrophic event</td>
<td>AIS</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>39 wk</td>
<td>345 g (&lt;10th percentile)</td>
<td>History of infertility</td>
<td>Placental abruption, ER C/S</td>
<td>Disseminated intravascular coagulation</td>
<td>Sudden catastrophic event</td>
<td>AIS</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>38 wk</td>
<td>584 g (90th percentile)</td>
<td>Primiparity, GBS positive (treated)</td>
<td>Prolonged rupture of membranes</td>
<td>Sepsis, disseminated intravascular coagulation</td>
<td>Thromboinflammatory process, decreased placental reserve</td>
<td>CSVT</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>37 + 5 wk</td>
<td>808 g (&gt;90th percentile)</td>
<td>Antepartum hemorrhage</td>
<td>FHR abnormalities, ER C/S, chorioamnionitis, ER C/S</td>
<td>Sepsis, anemia</td>
<td>Thromboinflammatory process, stressful intrauterine environment</td>
<td>CSVT</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>37 + 6 wk</td>
<td>452 g (25th percentile)</td>
<td>History of trauma</td>
<td>Ruptured uterus, placental abruption</td>
<td>Anemia, disseminated intravascular coagulation</td>
<td>Thromboinflammatory process</td>
<td>CSVT</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>34 wk</td>
<td>525 g (&gt;90th percentile)</td>
<td>None</td>
<td>Prolonged second-stage labor, FHR abnormalities, ER C/S</td>
<td>None</td>
<td>Sudden catastrophic event</td>
<td>CSVT</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>39 + 2 wk</td>
<td>500 g (50th percentile)</td>
<td>None</td>
<td>None</td>
<td>Congenital heart disease, postcardiac surgery</td>
<td>Sudden catastrophic event</td>
<td>CSVT</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>39 wk</td>
<td>581 g (75th percentile)</td>
<td>None</td>
<td>None</td>
<td>Polycythemia</td>
<td>Within normal limits</td>
<td>CSVT</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>40 + 2 wk</td>
<td>320 g (&lt;10th percentile)</td>
<td>None</td>
<td>FHR abnormalities, ER C/S</td>
<td>None</td>
<td>Decreased placental reserve, thromboinflammatory process</td>
<td>CSVT</td>
</tr>
</tbody>
</table>

IUGR indicates intrauterine growth restriction; ER C/S, emergency caesarian section; FHR, fetal heart rate.
3 had stem vessel thrombosis, and 1 had umbilical vein thrombosis. Such thrombi may ultimately travel into fetal circulation via the umbilical vein and into large cerebral blood vessels across the foramen ovale or ductus arteriosus, causing embolic cerebral arterial infarction.

Placental pathology suggesting decreased placental reserve was present in 3 of 12 patients. Placental insufficiency and infection can promote cytokine production, which may ultimately contribute to neonatal stroke. Cytokines are low-molecular weight signaling molecules. Placental trophoblasts and maternally derived leukocytes release proinflammatory cytokines at the placental-decidual interface, such as interleukin-6, interleukin-8, and tumor necrosis factor-α, in response to infection, vascular compromise, and oxidative stress.34–36 In rodents, decidual cytokines traverse the placental membranes and enter the fetal circulation, potentially affecting the developing fetus.37,38 In cases of clinical chorioamnionitis, cytokine concentrations in cord blood have been associated with abnormal neurologic examination and seizures.39 In vitro studies simulating hypoxia and growth restriction release excess tumor necrosis factor-α, which induces placental apoptosis. As a result, there is a disproportionate deposition of fibrin within the placental villus.40 Excess placental fibrin has the potential for thrombogenesis by converting endothelium from a thromboreistant to a thrombogenic surface, activating the coagulation cascade. Although the role of cytokines in neonatal brain injury remains unclear, they may play an important role in an inflammatory and coagulopathic response within placental and fetal circulation.

Nearly half the patients in our cohort had clinical and histologic features of a sudden catastrophic event, such as retroplacental hematoma or umbilical vessel occlusion. In addition, umbilical cord entanglements (cord overcoiling or abnormal insertion sites) were included in this group because they have been previously associated with cerebral palsy.21 Such lesions may lead to blood stasis and thrombus formation within umbilical vessels, allowing emboli access to fetal circulation. One

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placental Lesion Category</th>
<th>Placental Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Decreased placental reserve</td>
<td>Chronic villitis, distal villous immaturity, placental infarct, placental weight &lt;3rd percentile</td>
</tr>
<tr>
<td>2</td>
<td>Thromboinflammatory process</td>
<td>Chronic villitis, chronic intervillitis, villous edema, positive immunostaining for CD68+ cells</td>
</tr>
<tr>
<td>3</td>
<td>Thromboinflammatory process, stressful intrauterine environment</td>
<td>Chronic villous thrombosis, avascular fibrotic villi, increased nucleated red blood cells</td>
</tr>
<tr>
<td>4</td>
<td>Sudden catastrophic event</td>
<td>Cord overcoiling, distal villous immaturity</td>
</tr>
<tr>
<td>5</td>
<td>Sudden catastrophic event, thromboinflammatory process, decreased placental reserve</td>
<td>Velamentous cord insertion, cord venous congestion, chronic villitis, chronic intervillitis, placental infarction, distal villous immaturity, placental weight &lt;10th percentile</td>
</tr>
<tr>
<td>6</td>
<td>Thromboinflammatory process, stressful intrauterine environment</td>
<td>Funisitis (severe, diffuse), cord thrombosis (acute), cord venous congestion, severe chorioamnionitis, choricramic thrombosis, stem villous thrombosis, distal villous immaturity, villous chorangiosis</td>
</tr>
<tr>
<td>7</td>
<td>Sudden catastrophic event, thromboinflammatory process</td>
<td>Retropembranous hematoma, cord hemangioma, moderate chorioamnionitis, avascular fibrotic villi, distal villous immaturity</td>
</tr>
<tr>
<td>8</td>
<td>Placenta within normal limits</td>
<td>Villous edema</td>
</tr>
<tr>
<td>9</td>
<td>Sudden catastrophic event</td>
<td>Marginal cord insertion, stem villous thrombosis (acute), choricramnic thrombosis (acute)</td>
</tr>
<tr>
<td>10</td>
<td>Sudden catastrophic event</td>
<td>True cord knot and stricture, acute choricramnic thrombosis, cord thrombosis (acute) retromembranous hematoma</td>
</tr>
<tr>
<td>11</td>
<td>Placenta within normal limits</td>
<td>Choricramnic congestion, stem villous congestion, chronic villitis, placental infarct</td>
</tr>
<tr>
<td>12</td>
<td>Thromboinflammatory process, decreased placental reserve</td>
<td>Cord stricture, stem villous thrombosis (old and acute), choricramnic thrombosis (old), placental infarct, distal villous immaturity, placental weight &lt;10th percentile</td>
</tr>
</tbody>
</table>

**TABLE 3 Placental Pathology and Associated Lesional Category**

**FIGURE 1**
Hematoxylin and eosin stain of placental membranes demonstrating inflammatory cells within fetal membranes, consistent with acute chorioamnionitis (magnification ×200).
case report describes an acute umbilical artery occlusion resulting in aortic embolus in the fetus, in addition to multiple placental thrombi. Two patients in our study showed evidence of acute superimposed on chronic placental lesions. In these cases, acute abruption may be a consequence of underlying structural lesions in the placenta resulting in an inability to compensate for acute vascular injury. Previous studies also have shown that multiple placental lesions further increase the risk of later neurologic disability.

Limitations of this study include the lack of data on maternal thrombophilias and the absence of healthy newborn control subjects for comparison. Furthermore, our sample size is small and biased toward patients with a history of distress in labor or presentation within the first 24 hours of life, before disposal of the placenta. It is challenging to obtain placentas because most children with neonatal stroke will present clinically with seizures after 12 hours of life, at which point the placenta already may be discarded. Larger birthing centers may consider retaining placentas for 48 to 72 hours to allow for placental examination in neonates presenting with neurologic symptoms within the first few days of life.

CONCLUSIONS

We completed a detailed review of placental pathology and recognized risk factors for a series of selected patients with symptomatic neonatal stroke and suggested mechanisms underlying this disorder. The placenta may play an important role in thrombus formation and cytokine release, contributing to other risk factors for neonatal stroke. Although this is an important first look at the placenta in this population, a larger, prospective study comparing placentas from healthy newborns to those of distressed newborns is necessary to further establish the placenta as a causative factor in neonatal stroke.

REFERENCES

6. Amit M, Camfield PR. Neonatal polycythemia


