Cerebral Infarction as Multifocal Clonic Seizures in a Term Neonate

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Background: The incidence of neonatal stroke in full-term infants has been cautiously estimated as 1:10,000, but infants can initially have few symptoms, and the condition has the potential for underdiagnosis. Follow-up studies of known full-term neonatal stroke victims beyond 3 years of age indicate that most develop some form of hemiparesis, seizure disorder, cognitive difficulties, or developmental delay during childhood.

Methods: The case of a full-term infant who had a left middle cerebral artery infarction and who developed multifocal clonic seizures 9 hours after delivery is described and discussed.

Results: Head sonograms first showed evidence of disease when the infant was 72 hours old. Computed tomography (CT) of the head when the infant was 82 hours old showed an ischemic infarction in the distribution of the left middle cerebral artery. Subsequent magnetic resonance angiography showed a resolving embolus in the left middle cerebral artery.

Conclusions: Serial sonograms and CT scans of the infant's head, along with magnetic resonance angiography, were useful in making the diagnosis of cerebral infarction. A late intrauterine placental thromboembolus was the most likely cause. Maternal history of a previous cesarean section could be a risk factor. More studies are needed to define the incidence of this disease and to describe the risk factors.

Neonatal cerebral infarction is uncommon in full-term infants, and its incidence has been cautiously estimated as 1 in 10,000. Its true occurrence is unknown, however, as affected infants might have few symptoms of stroke, and the condition can easily go undiagnosed. Most victims of full-term neonatal stroke develop some form of hemiparesis, seizure disorder, cognitive difficulties, or developmental delay during childhood. It is important to recognize the indications of stroke in the full-term neonate and to learn whether certain risk factors are associated with this condition.

Methods
The case of a full-term infant with a left middle cerebral artery infarction is described and discussed in light of studies found with a MEDLINE search using the key words "neonate," "stroke," "infarction," and "seizure."

Neonatal Cerebral Infarction
In 1983 the English literature contained only about 5 reported cases of neonatal cerebral infarcts in living infants.1 By 1985, with the increased use of computed tomography (CT), the number of reported cases grew to 25, most of which involved full-term neonates.2 As of 1993, 81 cases of full-term neonates with strokes were found in the literature,3 and since then at least 14 more have been reported.4,5 Although most of these patients had seizures, neonatal stroke victims can initially have few symptoms.6-9 Subtle clinical appearance, an unsuspecting clinician, and early hospital discharge (before seizure onset) can allow many cases to go undiagnosed. In addition, sequelae of neonatal stroke, including seizure disorder, hemiparesis, cognitive difficulties, and developmental delays, often do not become apparent for years.4,9 Some children with these impairments could be expressing the latent effects of a previously undiagnosed neonatal stroke. Cerebral infarction in full-term neonates could be more common than is currently recognized. The purpose of this report is to provide information that will help raise awareness for the event and facilitate diagnosis and case management.

Case Report
The patient, a 3400-g baby boy, was born at 41 weeks' gestation to a 26-year-old mother (gravida
The differential leukocyte count was 44 bloody but showed clearing by the third tube. Findings on a chest radiograph were unremarkable, and the infant appeared to do well. A lumbar puncture showed an erythrocyte count of 24,500/μL, a leukocyte count of 5/μL (with 78 percent monocytes, 22 percent polymorphonuclear lymphocytes), protein 229 mg/dL, and glucose 57 mg/dL. The spinal fluid was initially bloody but showed clearing by the third tube.

Though minimal risk factors and nongenetic findings of laboratory studies made sepsis and meningitis seem unlikely, early infection could not be ruled out. Intravenous ampicillin was prescribed to treat infection by group B β-hemolytic streptococcus (the organism of primary concern) and cefuroxime for gram-negative bacteria. Both antibiotics were prescribed at dosages of 100 mg/kg every 12 hours. Cefuroxime was chosen rather than an aminoglycoside to avoid potential ototoxicity.

When the infant was 21½ hours old, he had a witnessed clonic seizure with synchronous jerking of both upper and lower extremities. One hour later he had an observed full multifocal clonic seizure. It was preceded by a 15- to 20-second episode of transient oxygen desaturation to 81 percent. As the oxygen saturation returned to normal, his right foot began twitching. Synchronous limb jerking followed in the order of right leg, left leg, then right arm. These movements could not be halted by restraint or passive flexion. During the event the infant was noted to be staring, and the Moro reflex was lost, but his ability to suck was maintained. With the exception of the heralding desaturation levels, oxygen saturation remained above 95 percent. A metabolic panel at the time of seizures showed blood glucose 80 mg/dL, sodium 139 mEq/L, potassium 4.6 mEq/L, chloride 111 mEq/L, carbon dioxide 21.0 mEq/L, blood urea nitrogen 7 mg/dL, creatinine 0.8 mg/dL, calcium 9.3 mg/dL, and magnesium 1.7 mg/dL. Results of toxicology screening of the infant's urine were negative for cocaine and other drugs. Intravenous phenobarbital was prescribed for seizure control.

There were no abnormalities on a sonogram of the infant's head when the infant was 24 hours old, and an electroencephalogram (EEG) when he was 48 hours old was nondiagnostic. The initial head CT scan done when the infant was 49 hours old, however, showed diffuse cerebral edema, slightly worse on the left, without midline shift. The patient was then transferred to a neonatal intensive care unit.

A second head sonogram when the infant was 74 hours old showed diffusely increased echogenicity within the left frontal and parietal lobes, as well as graying of adjacent sulci consistent with left hemispheric cerebral edema. There was no evidence of intraventricular hemorrhage. Results

His complete blood count showed a hemoglobin level of 16.6 g/dL, hematocrit 48.0 percent, platelets 344,000/μL, and a white cell count 24,500/μL. The differential leukocyte count was 80 percent segmented neutrophils, 1 percent band cells, 12 percent lymphocytes, and 7 percent monocytes. Findings on a chest radiograph were unremarkable. A lumbar puncture showed an erythrocyte count of 50/μL, a leukocyte count of 5/μL (with 78 percent monocytes, 22 percent polymorphonuclear lymphocytes), protein 229 mg/dL, and glucose 57 mg/dL. The spinal fluid was initially bloody but showed clearing by the third tube.
of a follow-up head CT scan when he was 82 hours old were diagnostic for infarction in the distribution of the left middle cerebral artery and suggested emboli, showing not only left hemispheric cerebral edema with subtle left to right midline shift, but also widened sulci in the right occiput. A cardiac sonogram showed no abnormalities. An EEG done on the third day of life showed sharp discharges at the vertex with generalization associated with a clinical tonic-clonic seizure lasting 2 minutes. Findings on a head sonogram when the infant was 98 hours old were unchanged from the previous scan. The patient remained hospitalized for seizure control and further diagnostic workup.

When the infant was 7 days old, magnetic resonance angiography showed findings consistent with a partially resorbed embolus in the left middle cerebral artery (Figure 1). Foci of decreased signal intensity in the left middle cerebral artery distribution and in the left basal ganglia were also noted on magnetic resonance imaging. All bacterial cultures were negative. Toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) titers and viral cultures yielded no positive results. Tests for protein C, protein S, and antithrombin III deficiencies were negative in both the parents and the baby. Anticardiolipin antibodies were not detected in either the mother or the baby. The placenta was not examined for pathologic changes. Throughout the hospitalization, the infant's blood pressure, which had been measured repeatedly,
Table 1. Causes of Seizures in Term Neonates.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Levy2 No.(%)</th>
<th>Lien3 No.(%)</th>
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<tbody>
<tr>
<td>Hypoxic events</td>
<td>26 (52)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>7 (14)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Cerebral malformation</td>
<td>3 (6)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>3 (6)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>2 (4)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Drug withdrawal</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (14)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Total</td>
<td>50 (100)</td>
<td>40 (100)</td>
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was in the normal range. The patient was discharged when 8 days old, seizure free, with a phenobarbital level of 43.3 μg/mL.

He did well until he was 2½ months old, when he had a brief seizure lasting approximately 1 minute during a mild febrile illness. His phenobarbital level was subtherapeutic at 8 μg/mL, so his dosage was increased to 5 mg/kg/d. At the age of 3 months he has had no further seizures.

Discussion

Clinical Presentation

In 1993 a retrospective study of more than 60,000 infants reported the incidence of early-onset seizures in full-term neonates to be 7:10,000, with 17.5 percent of these seizures caused by cerebral infarcts.5 The initial symptoms for most full-term neonates with diagnosed infarctions have been seizures, and among these, focal seizures were easily the most common. We found only one other report of a neonatal stroke in a full-term infant whose symptoms were multifocal clonic seizures,6 but some authors might classify this type of seizure within the broader category of focal seizures. Though the differential diagnosis for neonatal seizures is extensive,10 two unrelated studies2,5 on the cause of seizures in full-term neonates, done 10 years apart, showed remarkably similar results (Table 1). Both studies indicated that in the absence of a serious hypoxic event, cerebral infarction should be considered first in the differential diagnosis. Other signs of neonatal infarction can be more subtle and include lethargy, inactivity, absent suck, apnea and bradycardia, temperature instability, gaze palsies, spastic hemiparesis, or microcephaly.6,8,9,11-14

Diagnostic Studies

Sonographic studies of the head when screening for cerebral infarction were found to be valuable as early as 1983, when focal areas of increased echodensity were shown to correlate well with head CT scan findings in neonates with strokes.11 While some authors have reported poor success with head sonography,5,6 others have been so confident in its use that they omit performing a CT scan in the face of normal findings on serial head sonograms.15 Given that unequivocal findings of stroke can take 4 to 12 days to develop,12 the abnormal findings that appeared relatively early on a head sonogram, when the infant in our report was 74 hours old, increases the likelihood of a late intrauterine event. Serial scans were necessary because a scan 2 days earlier showed no abnormalities.

The evolutionary pattern of stroke seen on a head CT scan is similar for full-term neonates and adults. Findings are often normal for 2 to 3 days to 1 week following a large-vessel occlusion.16 Our patient's initial head CT scan when he was 49 hours old showed changes consistent with vasogenic edema known to occur 6 hours to 6 days after stroke,3 and the findings on a scan when he was 82 hours old were diagnostic, again pointing to a late intrauterine or very early postnatal event. Although finding two affected areas on a head CT scan (left hemisphere and right occiput) is consistent with embolic injury, the right occiput could have been an area of subcortical vulnerability to ischemia17 that was damaged by repeated hypoxic episodes occurring with the seizures that resulted from the initial left middle cerebral artery infarction.

Findings on magnetic resonance angiography confirmed left middle cerebral artery infarction but did not show the expected occlusion of distal branches of the right posterior cerebral artery as suggested by the right occipital involvement seen on the head CT scan. Angiography by magnetic resonance imaging is restricted to larger vessels,12 and detection of emboli in this area might not have been possible.

In most cases of neonatal stroke where EEGs were obtained, abnormal results were reported that often correlated well with CT findings. Though our patient's EEG confirmed seizure activity, it did not localize the involved area as well as did the head CT scan.
Table 2. Causes of Neonatal Arterial Stroke.

<table>
<thead>
<tr>
<th>Cause</th>
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<tr>
<td>Bacteremia and intravascular coagulation</td>
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<tr>
<td>Birth asphyxia</td>
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<tr>
<td>Birth trauma</td>
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<tr>
<td>Embolism</td>
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<tr>
<td>From the ducus arteriosus</td>
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<tr>
<td>From the heart</td>
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<tr>
<td>Through the heart</td>
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<tr>
<td>From the placenta</td>
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<tr>
<td>From systemic veins</td>
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<tr>
<td>During extracorporeal membrane oxygenation</td>
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<tr>
<td>From a temporal artery catheter</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Maternal cocaine abuse</td>
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<tr>
<td>Polycythemia</td>
</tr>
<tr>
<td>Postnatal asphyxia</td>
</tr>
<tr>
<td>Severe respiratory distress</td>
</tr>
<tr>
<td>Vasculitis (meningitis)</td>
</tr>
<tr>
<td>Bacterial</td>
</tr>
<tr>
<td>Viral</td>
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Etiology
Most cerebral infarcts in full-term neonates are ischemic and involve a middle cerebral artery, more commonly the left.3,18 Autopsy of 29 nonsurviving neonatal stroke victims (14 of whom had a gestational age of 38 weeks or more) showed that embolization was the most common cause of arterial occlusion.18 In our case, evidence of embolization by CT and magnetic resonance angiography, the inability to tolerate labor, early onset of symptoms, and relatively early abnormal findings on a head sonogram and CT scan point to an antenatal thromboembolic event. We believe the placenta was the most likely embolic source.

Other causes listed in Table 23 are not well supported or can be ruled out. The absence of murmur on initial physical examination and normal echocardiogram findings (obtained on the third day of life) make patent ducus arteriosus or cardiac defects an unlikely source of emboli. There were no clinical indications of a systemic vein thrombosis. Extracorporeal membrane oxygenation was not used, nor were any temporal artery catheters placed. The results of all bacterial and viral studies were negative or nondiagnostic. Normal hematocrit ruled out polycythemia. Cord gases were not consistent with birth asphyxia, and birth trauma was minimal as a result of a cesarean section delivery. The infant's blood pressure was not elevated, there was no evidence of severe respiratory distress before symptom onset, and outcome of a drug-screening test on the baby was negative. Early postnatal asphyxia is possible, perhaps from aspiration, as a barium swallow on the second day of life showed considerable reflux. Asphyxia is less consistent with the overall clinical picture, however, and would not explain the baby's inability to tolerate labor.

In addition to the causes listed in Table 2, antiphospholipid antibodies have been associated with fetal stroke,14 but in our case the mother and infant tested negative for these antibodies. Heritable coagulation defects were also considered, but test findings for protein C, protein S, and antithrombin III deficiencies were negative for both parents and the baby.

Risk Factors
Based on an analysis of 7 full-term neonates with strokes, risk factors for cerebral infarct have been described as postdates (gestation 41 weeks or longer, occurring in 4 of 7 cases), and advanced maternal age (35 years or older, occurring in 2 of 7 cases).5 Two of the 7 also involved a mother who had a history of cesarean section. We reviewed the literature to see how often an obstetric history of cesarean section was reported in full-term neonates with strokes. Including our own report, only 13 cases could be found where an obstetric history was addressed.5,8,11,13,16 In 5 of these 13 cases, the mother had had a previous cesarean section, making us suspect cesarean section as a possible risk factor for neonatal stroke. Perhaps suboptimal placental implantation over an area of previous uterine scarring predisposes to a small focus of placental abruption that is well contained by the surrounding well-implanted placenta but results in thrombus formation that could serve as a source of emboli.

Outcome
An outcome study of neonatal strokes in 16 full-term infants observed for an average age of 3 years and 2 months concluded that in the short term most seemed to do well.9 Symptoms of stroke in a newborn can initially be few, however, and take months or years to become fully expressed.4,9 Subsequent reports with longer fol-
low-up periods were less encouraging, indicating that most patients had hemiparesis, seizures, cognitive difficulties, or developmental delays.4,12

**Future Studies**

Some older children who display the above impairments could actually be manifesting the latent effects of a previously undiagnosed neonatal stroke. Because large intracranial thromboembolic accidents invariably result in areas of cavitation and porencephalic cysts,17 leaving a marker of the event, head CT scans on these children should show evidence of any earlier infarction. In a Swedish study of children between the ages of 6 and 15 years who were born at term and later had congenital hemiplegia diagnosed, 20 percent had evidence of cavitation on their head CT scan.12 From this study the incidence of arterial stroke in full-term neonates was cautiously estimated to be 1:10,000.3 Similar studies of children with other latent symptoms of neonatal cerebral infarction might also show CT evidence of earlier stroke.

Actual incidence of the disease could be much greater than the above estimate. Because many children with seizure disorder might have already had a CT scan of the head, retrospective studies would be relatively easy to conduct. Studies of children with developmental and cognitive deficits could be more difficult, because screening patients with mild impairments by head CT scanning could prove costly and nonproductive. Nevertheless, a direct relation between extent of cerebral damage and neuropsychologic test results has been shown for victims of neonatal stroke.12 A neuropsychologic screening test could be used to distinguish which impaired children would be most likely to have areas of infarction-associated cavitation on a head CT scan. Until such studies are conducted, the true incidence of cerebral infarction in full-term neonates will not be precisely known.

Further studies of risk factors, particularly maternal history of cesarean section, would also be beneficial. If the actual incidence of neonatal stroke in full-term infants turned out to be relatively high and a history of cesarean section were known to be a true risk factor, there could one day be a role for some type of antepartum fetal stroke prophylaxis in a subset of patients ascertained to have fetuses at high risk.

**Conclusions**

Cerebral infarction in full-term neonates is a problem that has not been fully delineated. Its symptoms usually are seizures, but there can be few symptoms and a resulting potential for underdiagnosis. Sonograms and CT scans of the head are useful diagnostic tools, though serial studies are often required.

Although many causes of cerebral infarction are recognized, embolism has been shown to be the most common cause at autopsy. Temporal aspects of the clinical symptoms, findings of the sonographic and CT scans of the infant's head, and magnetic resonance angiography results indicate that a late intrauterine placental thromboembolism most likely caused the stroke in our patient. Postdates and advanced maternal age are risk factors, but maternal history of cesarean section with an earlier pregnancy could also be a contributing factor. Though many victims are asymptomatic after the neonatal period, most show impairments later in early childhood (usually after 3 years of age) such as seizure disorders, hemiplegia, cognitive deficits, or developmental delays. The potential benefits from further study of this disease might, like the incidence of the condition itself, be underappreciated.

**References**