

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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## Case 12-2008: A Newborn Infant with Intermittent Apnea and Seizures

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### PRESENTATION OF CASE

A 1-day-old female infant was admitted to the neonatal intensive care unit of this hospital because of intermittent apnea and cyanosis. The day before admission, the patient was born at another hospital at 41 weeks 4 days' gestation to a 33-year-old primigravid mother. After 44 hours of labor, during which the amniotic membranes were artificially ruptured (17 hours before delivery) and the mother's temperature rose to 38.0°C, with a white-cell count of 26,700 per cubic millimeter, a cesarean section was performed because of failure of labor to progress. The infant weighed 4176 g (90th percentile) at birth, and the Apgar scores were 8 at 1 minute and 9 at 5 minutes.

At the other hospital, the infant was admitted to the newborn nursery, where she received care, including ophthalmic erythromycin. At the parents' request, vitamin K was not given. Results of laboratory tests are shown in Table 1. Approximately 24 hours after birth, several episodes of apnea occurred, associated with cyanosis of the skin, lips, and mucosal membranes, and the oxygen saturation fell to 70%. Stimulation and blow-by oxygen were administered, and the infant was transferred to the special care nursery. During the next 2 hours, three additional episodes of apnea and cyanosis were observed, associated with oxygen desaturation (50 to 60% saturation) and bradycardia (60 to 70 beats per minute). Neither lip-smacking nor abnormal movements were seen. The trachea was intubated. A chest radiograph showed the endotracheal tube above the carina and clear lung fields. A specimen of blood was sent for culture, and ampicillin and gentamicin were administered intravenously. Morphine sulfate (0.1 ml per kilogram of body weight) was administered intravenously, and the infant was bag-ventilated by hand, with 21% inspired oxygen and minimal pressures, at a rate of 30 breaths per minute. She was transferred to this hospital by ambulance and admitted to the neonatal intensive care unit.

The mother had received routine prenatal care. The maternal blood type was O, Rh-positive; results of screening tests for hepatitis B surface antigen, syphilis, group B streptococcus, and rubella were negative. There was a family history of

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**Table 1. Results of Laboratory Tests.\***

Variable	Reference Range (Age-Adjusted)†	First Hospital (1 Day after Birth)	On Admission (2 Days after Birth)	Day 2 (3 Days after Birth)	Day 4 (5 Days after Birth)
Hematocrit (%)	42.0–60.0 (birth–3 days of life), 45.0–67.0 (3–7 days of life)	55			43.1
Hemoglobin (g/dl)	14.5–22.5 (3–7 days of life)				14.6
White cells (per mm <sup>3</sup> )	9000–30,000 (birth–24 hr of life), 9400–34,000 (1–7 days of life)	22,000			8,800
Differential count (%)					
Neutrophils	66–87 (birth–24 hr of life), 53–62 (1–7 days of life)	54			54
Lymphocytes	22–37 (birth–24 hr of life), 21–34 (1–7 days of life)	18			31
Monocytes	4–11				11
Eosinophils	0–8				4
Band forms	<10	15			
Myelocytes		1			
Metamyelocytes		3			
Platelets (per mm <sup>3</sup> )	150,000–450,000	202,000			236,000
Partial-thromboplastin time (sec)	25.3–48.3 (3 days after birth), 22.1–54.0 (5 days after birth)‡			41.9	34.7
Prothrombin time (sec)	10.1–15.4 (3 days after birth), 10.0–14.8 (5 days after birth)‡			24.1	13.2
Lupus anticoagulant	Negative			Negative	
International normalized ratio					1.1
Glucose (mg/dl)§	60–100		113	97	94
Sodium (mmol/liter)	135–145		143	133	134
Potassium (mmol/liter)	4.0–5.6		4.9	3.8	3.5
Chloride (mmol/liter)	98–106			99	102
Urea nitrogen (mg/dl)§	5–20				3
Creatinine (mg/dl)§	0.3–1.0				0.5
Calcium (ionic) (mmol/liter)	1.14–1.30		1.27		1.21
pH, arterial	7.35–7.45		7.39¶	7.45¶	7.46¶
Partial pressure of oxygen, arterial (mm Hg)	60–80		59¶	109¶	102¶
Partial pressure of carbon dioxide, arterial (mm Hg)	30–35		36¶	33¶	35¶
Bicarbonate, arterial (mmol/liter)	19–22		21¶	23¶	24¶
Antithrombin III, functional (%)	39–88			78	
Protein C, functional (%)	17–53			27	
Activated protein C resistance (ratio)	>2.0			2.4	
Protein S, functional (%)	12–60			19	
Prothrombin gene mutation G20210A	Not present			Not present	
Homocysteine (μmol/liter)	0–12			3.6	
Anticardiolipin antibody					
IgG phospholipid units	0–15			5.1	
IgM phospholipid units	0–15			4.5	

Table 1. (Continued.)

Variable	Reference Range (Age-Adjusted) <sup>†</sup>	First Hospital (1 Day after Birth)	On Admission (2 Days after Birth)	Day 2 (3 Days after Birth)	Day 4 (5 Days after Birth)
Lipoprotein A (nmol/liter)	<75				15
17-OH-progesterone (ng/ml)	<50 for newborns <sup>**</sup>				<13.5
Biotinidase (%)	≥30 <sup>**</sup>				>30
Immunoreactive trypsinogen (%)	<95.1 <sup>**</sup>				17.9
Galactose, total (mg/dl)	<14 <sup>**</sup>				<2
Hemoglobin isoelectric focusing	FA, AF, or A <sup>**††</sup>				FA
Methionine (mg/dl)	<1.5 <sup>**</sup>				<1.5
Thyroid-stimulating hormone (μU/ml)	<15 (age-dependent) <sup>**</sup>				<2.5
Thyroxine (μg/dl)	>5.0 <sup>**</sup>				12.0
Leucine (mg/dl)	≤4.5 <sup>**</sup>				<4.5
Octanoylcarnitine (μM)	<0.80 <sup>**</sup>				<0.80
Phenylalanine (mg/dl)	≤2.3 <sup>**</sup>				≤2.3
Toxoplasma IgG (optical density)	<0.1 <sup>**</sup>				0.005

\* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted and are for persons who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

‡ The normal range in newborns and infants is an estimate derived from published normal ranges for these age groups and was not determined at Massachusetts General Hospital.

§ The fraction of inspired oxygen was 21%.

¶ The fraction of inspired oxygen was 99%.

|| A normal result on a screening test for activated protein C resistance indicates no laboratory evidence of the factor V Leiden mutation.

\*\* Reference ranges for newborns are from the New England Newborn Screening Program, Jamaica Plain, Massachusetts.

†† FA denotes hemoglobin that is more fetal than adult, AF hemoglobin that is more adult than fetal, and A hemoglobin that is entirely adult.

pulmonary embolus, but there were no neurodevelopmental disorders, clotting disorders, or unexplained infant deaths.

On examination, the infant appeared well. The weight was 4070 g, and the head circumference 34.8 cm. The temperature was 37.3°C, the pulse 125 beats per minute, the respiratory rate 35 breaths per minute, and the oxygen saturation 99% while the patient was breathing 21% oxygen with conventional mechanical ventilation set at 25 breaths per minute; the peak inspiratory pressure was 16 cm of water, and the end-expiratory pressure was 5 cm of water. There were no dysmorphic features. Mild edema was present over the left side of the temporoparietal scalp. The anterior fontanel was open and full, and the suture lines were normal. The eyes opened spontaneously, tracked to the examiner's face, and closed to penlight stimulation. All limbs moved spontaneously; there was bilateral hypertonia with no clonus. Deep-tendon reflexes

were brisk. The Moro reflex was present, the snout sign was negative, and the Babinski reflex was present in both feet. The remainder of the examination was normal. Results of laboratory tests are shown in Table 1. A chest radiograph was normal. Intravenous fluid (10% glucose and water) was administered. During initial bedside electroencephalographic (EEG) monitoring that lasted an hour, with the patient in wakeful, active, and quiet sleep states, no apneic events occurred. The left hemisphere showed slightly excessive theta activity; there was no evidence of seizure.

Computed tomographic (CT) scanning of the brain without the administration of contrast material revealed relative hypodensity of the anterior left temporal lobe, involving the superior temporal gyrus and extending into the middle temporal gyrus. There was no intracranial hemorrhage or hydrocephalus. Magnetic resonance imaging (MRI) of the brain con-

## DIFFERENTIAL DIAGNOSIS

firmed a subtle increase in T<sub>2</sub>-weighted signal, with loss of differentiation between gray and white matter in the left temporal lobe that involved the superior and middle temporal gyrus, a finding that was consistent with gyral edema, with a corresponding wedge-shaped region of decreased diffusion. Collectively, these findings were believed to be consistent with acute arterial ischemic injury of the left temporal lobe in the distribution of the left middle cerebral artery.

During the first night in this hospital, a 10-second episode of leftward nystagmus occurred that was accompanied by a fall in the respiratory rate to 28 breaths per minute, without tonic-clonic movements or oxygen desaturation. Several additional self-limited episodes of bradypnea occurred that lasted less than 30 seconds.

On the second hospital day, continuous EEG monitoring showed frequent sharp waves in the left temporal lobe, where there was also seizure activity, both with and without accompanying apnea; there was no clinical evidence of seizures. An episode of bradypnea occurred, with oxygen saturation of 81% and cyanosis; the bradypnea resolved spontaneously, and phenobarbital (loading dose, 20 mg per kilogram) was administered. The blood cultures obtained at the other hospital were reported to be negative, and antibiotics were discontinued. On the second and third hospital days, the oxygen saturation fell to 81 to 86% intermittently, with no corresponding change in the respiratory rate. Seizure activity continued to appear on the EEG tracing; additional phenobarbital (10 mg per kilogram) was given, followed by the administration of fosphenytoin, and encephalographic seizure activity ceased. Results of laboratory tests from day 2 are shown in Table 1. Vitamin K was administered subcutaneously. An echocardiogram on the third hospital day showed thickening of the tricuspid leaflets, with a thin, mobile, linear echodensity that prolapsed into the right atrium, findings that were consistent with a vegetation or thrombus on the valve, as well as a patent foramen ovale with right-to-left shunting.

Fosphenytoin was discontinued on the fourth day; continuous EEG monitoring was stopped, and the trachea was extubated. Anticoagulation with low-molecular-weight heparin was begun. An EEG obtained on the fifth day showed no seizure activity.

A diagnostic test was performed.

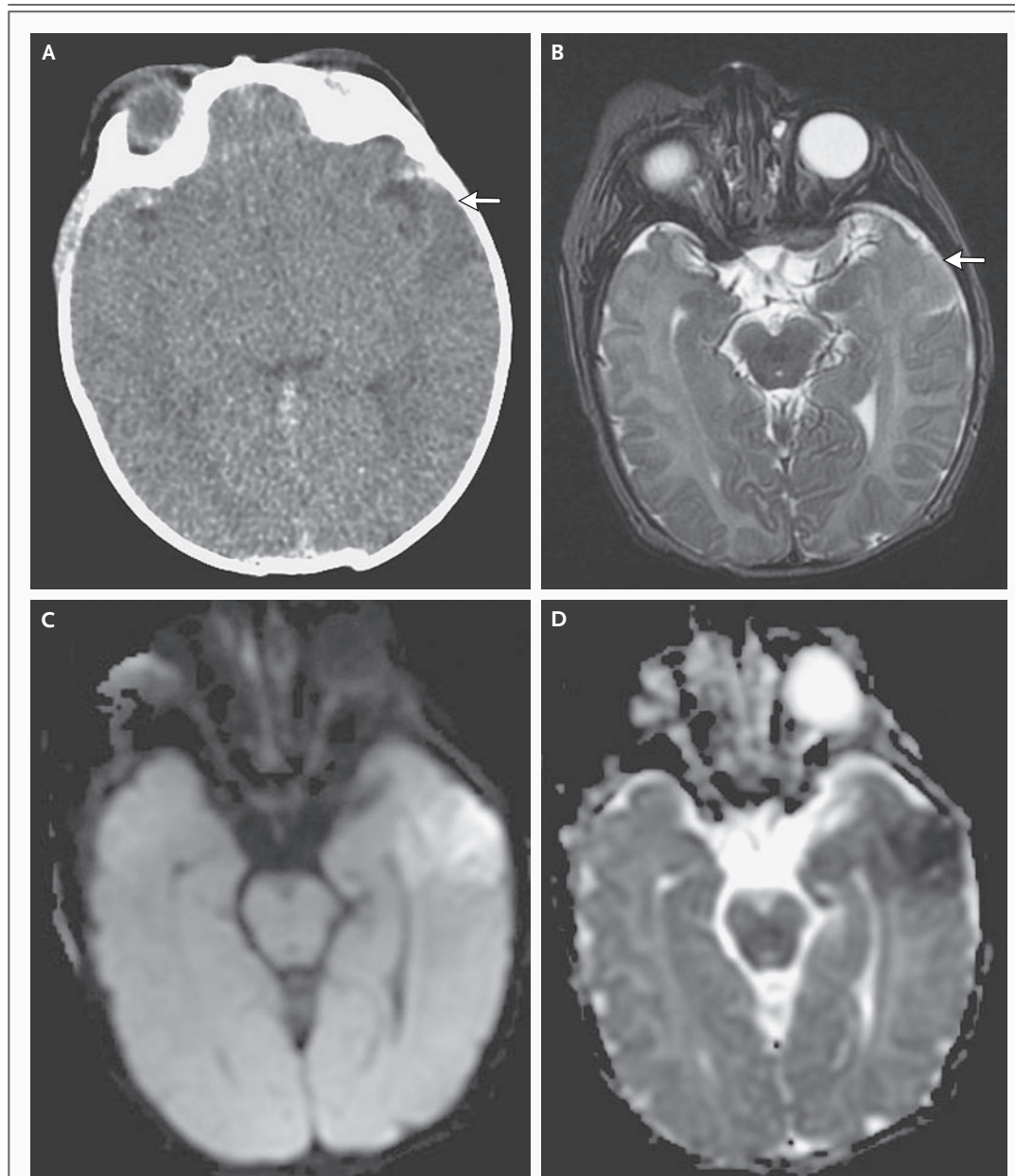
*Dr. Raymond W. Redline:* May we see the EEG and imaging studies?

*Dr. Kalpathy S. Krishnamoorthy:* A 24-hour bedside EEG, obtained when the baby was having multiple apneic events (see Fig. 1 of the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)), shows runs of high-voltage sharp waves coming predominantly from the left temporal region, lasting for more than 10 seconds; this pattern is considered an EEG hallmark of seizure. Similar runs occurred almost every 5 to 10 minutes for the next 18 hours, which were consistent with frequent seizures. Many of these results were not correlated with any clinical evidence of seizure activity. Since the absence of a correlation between EEG and clinical findings is not uncommon, in difficult cases, continuous bedside EEG can be helpful in deciding on appropriate therapy.

Because of the EEG evidence of seizures, the child was given anticonvulsant agents intravenously; after 6 to 8 hours, EEG evidence of seizure disappeared, indicating a response to treatment. A follow-up standard EEG obtained 3 days later was normal.

*Dr. Pallavi Sagar:* CT scanning of the brain on the first hospital day without the administration of contrast material showed no evidence of hydrocephalus, intracranial hemorrhage, brain malformation, or mass lesion. However, a subtle hypodensity in the left temporal lobe (Fig. 1A) raised concern about acute ischemic injury. The same day, an MRI study of the brain (Fig. 1B) confirmed the presence of a wedge-shaped area of loss of differentiation between gray matter and white matter in the left temporal lobe corresponding to the abnormality on the CT scan of the brain, which was consistent with edema. Diffusion-weighted imaging (Fig. 1C) showed restricted diffusion, with decreased apparent-diffusion-coefficient values (Fig. 1D) suggestive of cytotoxic edema. These findings are consistent with acute arterial ischemic stroke in the distribution of the left middle cerebral artery.

*Dr. Mary Etta King:* The echocardiogram shows diffuse thickening of the septal leaflet of the tricuspid valve (Fig. 2A and Video 1 of the Supplementary Appendix). In some views, there is a small, linear, prolapsing structure associated with the area of thickening (Fig. 2A and Video 2 of the

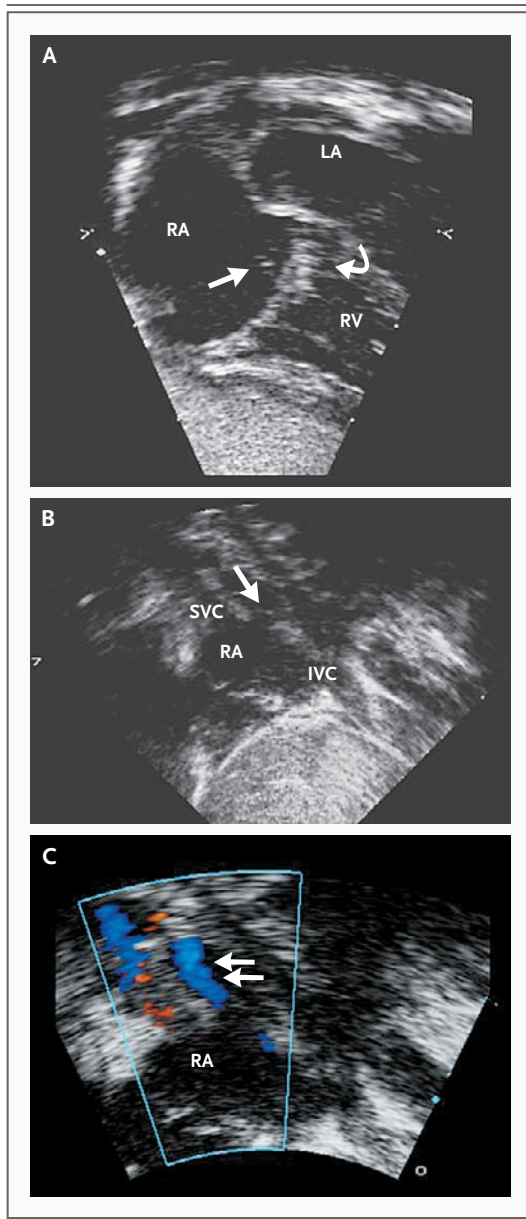


**Figure 1. CT and MRI Studies of the Brain.**

An axial CT scan obtained without contrast enhancement (Panel A) shows a subtle wedge-shaped hypodensity in the left temporal lobe (arrow). An MRI scan (Panel B) shows an increased  $T_2$ -weighted signal, with loss of differentiation between gray and white matter (arrow). There is corresponding decreased diffusion, with reduced apparent-diffusion-coefficient values on diffusion-weighted imaging (Panel C) and the apparent-diffusion-coefficient map (Panel D) involving the left temporal lobe. These findings are consistent with acute arterioischemic stroke in the left middle cerebral artery distribution.

Supplementary Appendix). This may represent a fibrin strand, thrombus, or vegetation associated with the valve. There is a patent foramen ovale (Fig. 2B and Video 3 of the Supplementary Appen-

dix), as seen in nearly all newborns, with evidence of intermittent right-to-left shunting on color Doppler imaging (Fig. 2C and Video 4 of the Supplementary Appendix). Since the pressures in the



**Figure 2. Echocardiographic Images.**

A two-dimensional subcostal echocardiographic view of the right atrium and tricuspid valve shows diffuse thickening of the septal tricuspid leaflet (Panel A, curved arrow) as well as a linear mobile structure that prolapses into the right atrium (straight arrow). In these images, the valve, which should be linear and thin, appears shaggy and highly reflective. A two-dimensional subcostal, bicaval view of the right atrium shows the interatrial septum, with a thin mobile septum covering the fossa ovalis (Panel B); there is transient leftward displacement of the flap valve of the fossa ovalis (arrow). The color Doppler image (Panel C) shows intermittent right-to-left shunting, with the passage of flow from the right atrium to the left atrium as the septum moves slightly with changes in the interatrial pressures (blue flow jet, double arrows). IVC denotes inferior vena cava, LA left atrium, RA right atrium, RV right ventricle, and SVC superior vena cava.

#### CHORIOAMNIONITIS

Long labor, a prolonged period between artificial rupture of the membranes and delivery, maternal fever, a high maternal white-cell count, and a ratio of immature to total neutrophils in the newborn that is at the upper limit of the normal range are suggestive, but not diagnostic, of chorioamnionitis in this case.<sup>1</sup> Chorioamnionitis is an infection of the placental membranes usually caused by organisms spreading to the uterus from the lower genital tract. The clinical diagnosis of chorioamnionitis has high false negative and false positive rates as compared with the gold standard, placental histopathological diagnosis.<sup>2</sup>

#### APNEIC SPELLS

Apneic spells, defined as cessation of respirations for 15 to 20 seconds or more in the first 6 months of life, are frequently associated with oxygen desaturation and reflex bradycardia.<sup>3</sup> In preterm infants, the normal stimulation of respiratory drive triggered by transient arterial hypoxia and increased hypercapnia is commonly delayed, and prolonged periods of apnea can occur in the absence of a specific cause. In term infants, such as this one, apneic spells are usually observed in association with other abnormalities. Causes of apneic spells originating outside the central nervous system (CNS) include sepsis, genetic metabolic disorders, congenital heart disease, gastroesophageal reflux, and poor pharyngeal coordination. Causes that originate within the CNS include hy-

right side of the heart of a newborn are still somewhat high, there is the potential for right-to-left embolization through the patent foramen ovale.

*Dr. Redline:* This 1-day-old infant had unexplained episodes of apnea after birth by cesarean section at 41 weeks 4 days' gestation. The birth was complicated by prolonged labor, artificial rupture of the membranes 17 hours before delivery, and a maternal temperature of 38.0°C. This presentation could result from a number of conditions.

poventilation syndromes, parenchymal lesions, and seizures. In this patient, seizures were documented by EEG and were responsible for the episodes of bradypnea and apnea.

#### NEONATAL SEIZURES

Unlike seizures in later life, neonatal seizures are often brief and subtle.<sup>4</sup> They usually require EEG confirmation and have a distinct spectrum of eliciting factors. Causes of neonatal seizure not associated with the CNS include drug withdrawal, electrolyte imbalance, pyridoxine deficiency, and genetic–metabolic disorders. In this case, there was no history of maternal substance abuse or positive results of drug testing. Serum sodium, calcium, and glucose levels were normal, and the seizures responded to medication without pyridoxine supplementation. The list of inborn errors of metabolism associated with neonatal seizures is long. Most are characterized by hypotonia, lethargy, coma, or ataxia rather than the hypertonia and normal consciousness in this patient. Furthermore, localization of seizures to the left temporal lobe of the brain, normal screening laboratory values, a negative family history, and the absence of extra-CNS manifestations make these diagnoses unlikely.

Causes of seizures arising within the CNS include hypoxic–ischemic brain injury, maldevelopment of the CNS, and cerebrovascular lesions. This infant's Apgar scores were normal, and there were no signs or symptoms of neonatal encephalopathy, ruling out a hypoxic–ischemic event. Cerebrovascular lesions can affect veins or arteries. Venous lesions include sinus venous thrombosis, hemorrhagic infarction, and malformations. Arterial lesions include strokes due to occlusion of large or small arteries and global cerebral hypoperfusion, causing necrosis of tissue at the periphery of arterial vascular beds (known as watershed infarcts). Radiologic studies showed a lesion in the distribution of the left middle cerebral artery, a finding consistent with perinatal arterial stroke.

#### PERINATAL ISCHEMIC STROKE

The features of this case meet the defining criterion for perinatal ischemic stroke: focal disruption of cerebral blood flow due to arterial or venous thrombosis occurring between the 20th week of fetal life and the 28th postnatal day and confirmed by neuroimaging or neuropathological studies.<sup>5</sup> Neonatal stroke is the most common

known cause of cerebral palsy in term infants such as this one. Although rare cases are caused by malformed or damaged blood vessels or infectious vasculitis,<sup>6</sup> these causes are especially uncommon in the early perinatal period and thus are unlikely in this case. The remaining cases are attributable to thromboembolic disease, the probable diagnosis here. Thromboembolic lesions most commonly affect the left middle cerebral artery, possibly reflecting a more direct route of spread to this artery through a patent foramen ovale than to other cerebral arteries. This patient had no obvious risk factors for thromboembolic disease, such as indwelling catheters or cardiac malformations. Among the multiple risk factors (Table 2), those most relevant to this case are fetal thrombophilia, neonatal infection, and thromboinflammatory disorders of the placenta.

#### Fetal Thrombophilia

As in adult and pediatric stroke, underlying thrombotic disorders are important risk factors for

**Table 2. Risk Factors for Perinatal Ischemic Stroke.\***

Maternal and fetal thrombotic and coagulation disorders
MTHFR, factor V G1691A, factor II G2021A mutations
Increased factor VIII, homocysteine levels
Lp(a) lipoprotein, antithrombin III, and protein C and S deficiencies
Other maternal and fetal factors and conditions
Preeclampsia
Chorioamnionitis
Birth asphyxia
Maternal autoimmune conditions and autoantibodies (PLA-1 antigen)
Maternal antiphospholipid syndrome
Placental disorders
Fetal and neonatal disorders and conditions
Vascular malformations
Inherited thrombophilias (as above, plus 5,10-MTHFR mutations, decreased antithrombin III, protein C antigen or activity, or protein S antigen)
Twin–twin transfusion syndrome
Fetal or neonatal polycythemia
Congenital heart disease
Indwelling catheters
Persistent fetal circulation and extracorporeal membrane oxygenation therapy
Fetal or neonatal infections and meningitis

\* Information is from Raju et al.<sup>5</sup> MTHFR denotes methylenetetrahydrofolate reductase.

perinatal stroke. The only maternal thrombophilias implicated in neonatal stroke are diseases associated with IgG antiphospholipid antibodies, which can cross the placental barrier. In this case, there was no history of maternal antiphospholipid antibody syndrome or connective tissue disease. Neonatal abnormalities associated with perinatal arterial stroke that could be considered in this case include those that may occur in the mother and others listed in Table 2.<sup>6</sup> Despite the family history of pulmonary embolism, the mild transient elevation in the patient's prothrombin time, and the possible thrombus on the tricuspid valve, testing in this case failed to reveal any of these abnormalities. Nonetheless, since levels of coagulation and anticoagulation factors in the neonatal period differ markedly from levels later in life, repeated and extended testing of mother and fetus after the perinatal period should be considered in this case.

#### Neonatal Infection

Fetal and neonatal infections can be associated with high circulating levels of inflammatory cytokines, activated platelets, complement components, and decreased anticoagulant proteins that together can promote endothelial activation, platelet adherence, and development of thrombi.<sup>7</sup> Endocarditis might be a cause of the thrombus on the tricuspid valve in this infant, but such a condition is extremely rare in otherwise normal neonates. Local infections of the CNS, including meningitis, ventriculitis, and brain abscess, can lead to a local inflammatory response that can include thrombosis, but this response would generally involve smaller vessels. This infant's blood cultures were negative, and the lack of systemic symptoms of sepsis and the normal chest radiograph argue

against neonatal infection as a cause of stroke in this case.

#### Severe Placental–Fetal Vascular Lesions

Finally, thromboinflammatory processes affecting large fetal vessels in the umbilical cord, chorionic plate, and large stem villi have been found in children with cerebral palsy and other forms of long-term neurologic impairment, including stroke<sup>8</sup> (Table 3). These lesions can contribute to stroke in three ways: global impairment of placental function, leading to hypoxia and acidosis; release of inflammatory mediators that can promote a fetal coagulopathy; and formation of placental vascular thrombi that can embolize through the ductus venosus and foramen ovale to the cerebral arterial circulation.

Meconium-associated vascular necrosis<sup>9</sup> can be ruled out, since there was no meconium staining of amniotic fluid in this case. Chronic villitis with obliterative fetal vasculitis<sup>10</sup> is more commonly associated with diffuse CNS disease than with localized disease. Fetal thrombotic vasculopathy<sup>11</sup> is unlikely in the absence of fetal thrombophilia or chronic umbilical-cord obstruction. The most likely diagnosis in this case is thus acute chorioamnionitis with a severe fetal inflammatory response.<sup>12</sup> Although histologic evidence of chorioamnionitis is seen in 10 to 15% of term placentas, severe fetal inflammatory responses are much less common, are risk factors for neurologic impairment in both term and preterm infants,<sup>2</sup> and are, in my experience, the placental lesion most commonly seen in cases of spastic hemiplegia and perinatal stroke.<sup>13–16</sup>

My choice of diagnostic test would be pathological examination of the placenta.

**Table 3. Severe Fetal–Placental Thromboinflammatory Vascular Disorders.**

Diagnosis	Characteristics
Meconium-associated fetal vascular necrosis	Necrosis of the muscular wall of umbilical and chorionic-plate vessels as a result of prolonged exposure to the toxic effects of meconium
Chronic villitis with obliterative fetal vasculopathy	Fetal vasculitis involving stem villous vessels, resulting from maternal T lymphocytes that have crossed the placental barrier; more commonly associated with diffuse rather than localized central nervous system abnormalities
Fetal thrombotic vasculopathy	Formation of thrombi in fetal vessels of the umbilical cord, chorionic plate, or stem villi, resulting in downstream areas of involutational villous necrosis; occurs in cases of chronic umbilical-cord obstruction or fetal thrombophilia
Chorioamnionitis with severe fetal vasculitis	Intense umbilical or chorionic vasculitis, with or without associated thrombi, resulting from severe fetal inflammatory response; frequently seen in cases of spastic hemiplegia, perinatal stroke, and cerebral palsy



*Dr. Nancy Lee Harris (Pathology):* Dr. Krishnamoorthy, what was your thinking when you evaluated this patient?

*Dr. Krishnamoorthy:* The combination of apnea, oxygen desaturation, and cyanosis in a term infant suggested the diagnosis of recurrent subtle seizures, which were confirmed by continuous EEG monitoring. Since a common cause of subtle seizures is intracranial hemorrhage, especially subarachnoid hemorrhage with pooling in the temporal-lobe tips, I initially suspected an intracranial hemorrhage. In most cases, neonatal stroke is manifested as focal clonic seizures, so this condition was not as high on our list of diagnoses. However, imaging studies revealed evidence of a stroke. We requested that the placenta be sent from the other hospital for examination.

#### CLINICAL DIAGNOSIS

Neonatal stroke.

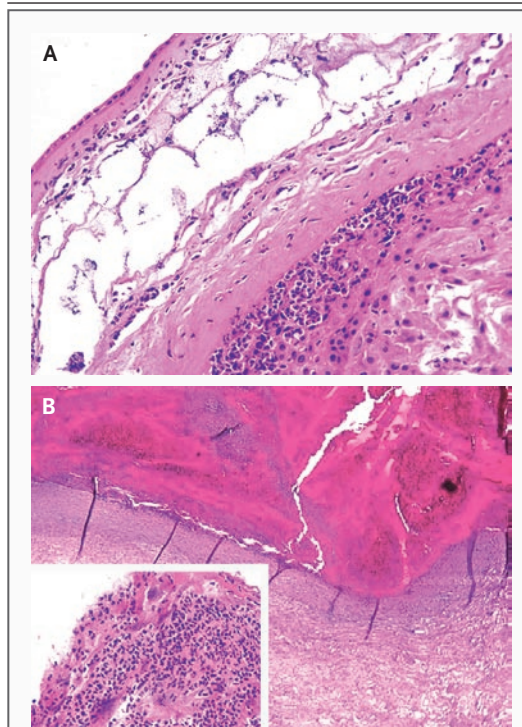
#### DR. RAYMOND W. REDLINE'S DIAGNOSIS

Neonatal stroke due to acute chorioamnionitis, with a severe fetal inflammatory response; superimposed neonatal sepsis or underlying thrombophilia to be ruled out.

#### PATHOLOGICAL DISCUSSION

*Dr. Drucilla J. Roberts:* The placenta had been frozen and was sent to us for examination. It weighed 660 g, and there was no gross abnormality. The cord was inserted eccentrically into the placenta, with no membranous vessels. It was normal in length and diameter, without abnormal spiraling or knots; the membranes were not appreciably discolored, and there were no masses in the parenchyma. Sections of the cord, membranes, chorionic plate, maternal floor, and parenchyma were obtained. Histologic examination revealed a normally developed, mature placenta with moderate acute chorioamnionitis (Fig. 3A); a severe, dramatic chorionic-plate vasculitis (Fig. 3B); and a mild umbilical-cord phlebitis (Fig. 3C). The diagnosis is acute chorioamnionitis with umbilical-cord phlebitis and intense chorionic-plate vasculitis.

*Dr. Harris:* Dr. Grabowski, would you like to comment on the management of this case?



**Figure 3. Sections of the Placenta (Hematoxylin and Eosin).**

A section through rolled membranes (Panel A) shows the presence of maternal neutrophils in the amniotic and chorionic tissues. The chorionic plate (Panel B) contains a chorionic vessel with a marked fetal inflammatory infiltrate traversing the vessel wall toward the amniotic cavity. High magnification of the umbilical vein (Panel B, inset) shows fetal neutrophils within the venous smooth muscle.

#### DISCUSSION OF MANAGEMENT

*Dr. Eric F. Grabowski:* As a member of the Pediatric Stroke Service, I was asked whether there was a need for anticoagulation in this case. Recurrent thromboembolic events are rare in neonates with arterial ischemic stroke, with such events reported in only 3% of the infants in one study.<sup>17</sup> This low rate reflects the predominance of perinatal and maternal factors, which do not persist after birth, in the case of neonatal stroke. Many neonates with recurrent stroke have at least one plasma-phase risk factor (e.g., factor V Leiden).<sup>17</sup> Although newborns with stroke usually do not require anticoagulant therapy, I would recommend its use, first, if there is a thrombus in the heart or in a major artery, especially in the presence of

a patent foramen ovale or atrial or ventricular septal defect; second, if there is a plasma-phase risk factor other than isolated factor V Leiden or the prothrombin gene mutation G20210A; and third, if there is radiologically confirmed progression or recurrence of stroke.

In this patient, despite a family history of pulmonary embolism, no plasma risk factor was found. The parents had declined administration of vitamin K after birth, which is given to correct the low levels of vitamin K–dependent clotting factors (factors II, VII, IX, and X) in newborns but which also corrects the low levels of anticlotting factors (proteins C, S, and Z). The withholding of vitamin K in this case may have allowed low levels of both factor types to persist. Vitamin K was given on the second hospital day, with normalization of the prothrombin time.

Although the thrombus that gave rise to this patient's stroke seems likely to have originated in the placenta, the picture was complicated by the echocardiogram, which showed thickening of the tricuspid leaflets and a prolapsing structure on the valve, findings that we interpreted as valvular thrombus, especially in view of the child's elevated level of D-dimer. Whether this thrombus also originated in the placenta or was formed in situ because of a hypercoagulable state, there was a risk that it would embolize to the brain through the patent foramen ovale. Thus, this patient met our criteria for use of anticoagulation therapy. We administered low-molecular-weight heparin (1.5 mg per kilogram), subcutaneously, twice daily for 3 months.

Follow-up echocardiography while the patient was receiving treatment with this regimen showed disappearance of the mobile thrombus at the time of discharge on the 11th hospital day; the thickening of the tricuspid valve had resolved by the 7th week. A patent foramen ovale was still present.

*Dr. Harris:* Dr. Krishnamoorthy, will you tell us how the patient is now?

*Dr. Krishnamoorthy:* I last saw her about 3 months after discharge. At that time, the phenobarbital had been stopped for about 6 weeks; there was no further evidence of seizure activity, and her neurologic examination was normal. Her pediatrician reported that she had achieved all the normal developmental milestones at 1 year of age and that her development was normal. Most infants with perinatal stroke have a good prognosis, without neurologic deficits, and achieve normal or close-to-normal milestones. This patient's parents declined further imaging studies, but in most patients, the lesions are actually reduced in size on follow-up MRI. In contrast, the prognosis is much worse in cases of antenatal stroke, occurring at a gestational age of less than 28 weeks. Larger areas of tissue loss can be seen on MRI, most patients have cerebral palsy with marked spasticity, and many have abnormal cognitive development.

#### ANATOMICAL DIAGNOSIS

Severe acute chorioamnionitis with umbilical-cord phlebitis and intense chorionic-plate vasculitis.

Dr. Grabowski reports serving on a scientific advisory board for Baxter Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.



Four videos showing echocardiographic views of the left and right atria are available with the full text of this article at [www.nejm.org](http://www.nejm.org).

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