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Clinical and laboratory observations

Perinatal cerebral infarction and maternal cocaine use

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The use of cocaine as a recreational drug has increased markedly in the United States in the last few years. Concomitantly, more women have used cocaine during pregnancy. Information on the effects of cocaine on the developing fetus, however, is sparse. We report an infant who developed cerebral infarction after delivery at term to a woman who used a large amount of cocaine in the 72 hours before delivery.

CASE REPORT

This white male infant was the 3660 gm product of a 40-week gestation born to a 32-year-old G2P0Ab1 (elective), blood type A, Rh-positive, VDRL-negative mother whose pregnancy was com-

See related article p. 459.

CT Computed tomography

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plicated by cocaine use intranasally during the first 5 weeks of pregnancy. She abstained from cocaine until the 3 days before delivery, during which she used 5 gm cocaine intranasally. On the day of delivery, the mother used approximately 1 gm cocaine

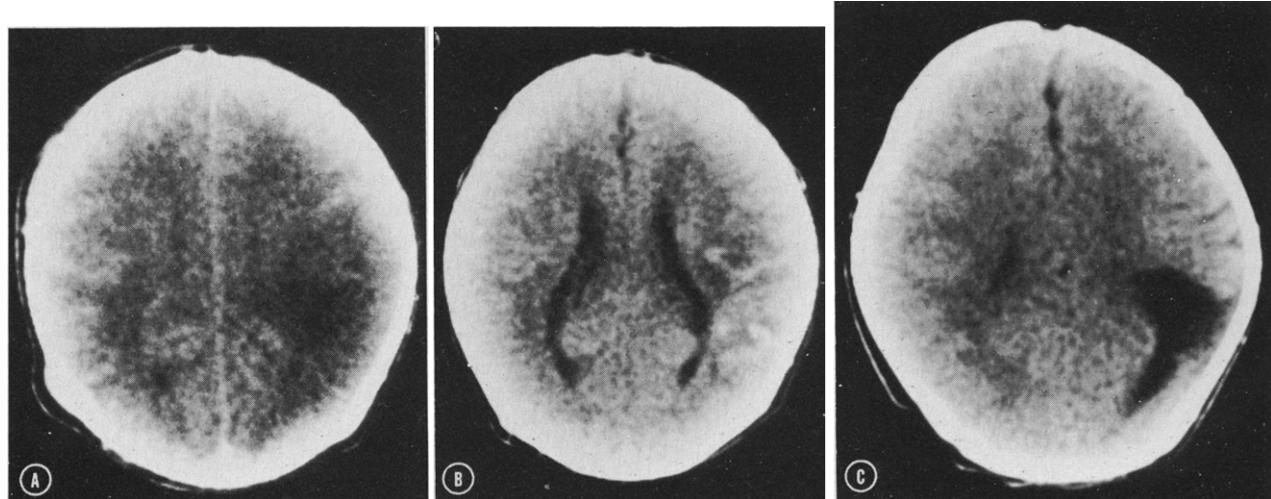


Figure. A, Noncontrast CT scan, 24 hours of age, showing decreased attenuation involving gray and white matter in left frontal parietal region. B, Noncontrast CT scan, 7 days of age, showing gyral type of increased density in region of previously described left parietal infarct and slight increase in ventricular size. C, Noncontrast CT scan, 2½ months of age, showing discrete area of focal hypodensity in region of previously described infarct, consistent with focal encephalomalacia or porencephaly.

intranasally, with the last dose reportedly taken 15 hours before delivery of the infant. Rupture of membranes and onset of contractions occurred during this period of time. On admission to the labor corridor, the mother was noted to be disoriented and to have slurred speech; she was described by the staff as intoxicated. Her heart rate was 120 beats per minute, and blood pressure was 124/80 mm Hg. Fetal monitoring during the 12 hours before delivery showed the infant to have multiple variable decelerations; the baseline fetal heart rate was 180 to 200 beats per minute. Meconium staining of the amniotic fluid was noted. Maternal urine obtained after delivery was positive on toxicologic screen for cocaine and nicotine. The urine was negative for opiates, alcohol, barbiturates, marijuana, amphetamines, benzodiazepines, propoxyphene, and phencyclidine.

Delivery occurred vaginally with epidural anesthesia; Apgar scores were 1 at 1 minute and 7 at 5 minutes. The infant was limp and had a heart rate of 80 beats per minute at birth; thick meconium staining was noted. The trachea was immediately intubated and suctioned; no meconium was found. Ventilation with 100% O₂ was transiently performed, which produced marked improvement. The endotracheal tubes were removed at approximately 5 minutes of age, and the infant remained pink, well-perfused, and vigorous, without respiratory distress. Arterial cord blood gas values were pH 7.30, PCO₂ 46 mm Hg, and base deficit -4; venous cord blood gas values were pH 7.32, PCO₂ 42 mm Hg, and base deficit -4.

The infant was transferred to the normal newborn nursery, where his initial physical examination was within normal limits except for mild decreased muscle tone of the right upper extremity and tachycardia as high as 180 beats per minute. At approximately 16 hours of age, he had several episodes of apnea and cyanosis. He was transferred to the high-risk nursery, where he was noted to

Table. Urine concentrations of cocaine metabolites

Age (hr)	Urine toxicology	Concentration (ng/mL)
24	Cocaine	
	Nicotine	
	Benzoylecggonine	1240
48	Benzoylecggonine	240
60	Benzoylecggonine	150
68	Benzoylecggonine	118
76	Benzoylecggonine	89
82	Benzoylecggonine	38
96	Benzoylecggonine	20
120	Negative	

have multiple focal seizures involving the right upper and lower extremities and a right parietal cephalohematoma. He had intermittent tachycardia to a rate of 180 beats per minute and a systolic blood pressure of up to 140 mm Hg by palpation. He had marked truncal hypotonia; decreased flexor tone in the right arm, shoulder, and hip; right-sided hyperreflexia; tight cortical thumbs bilaterally; and miotic pupils that dilated in response to noxious stimulation.

Diagnostic evaluation of this infant included the following studies. Blood glucose, electrolytes, urea, creatinine, magnesium, calcium and ammonium concentrations, complete blood count with white blood cell differential, and arterial blood gas values were normal. Platelet count was 212,000/ μ l. No coagulation studies were performed. Noncontrast computed tomography of the brain, done at 24 hours of age, showed an acute infarction in the distribution of the left middle cerebral artery (Figure). Cerebrospinal fluid evaluation at 21 hours of age showed 1800 red

blood cells and five white blood cells per microliter, glucose 81 mg/dl (113 mg/dl in plasma), protein 62 mg/dl, and a negative Gram stain. Urine toxicologic studies at 24 hours of life after treatment with phenobarbital and phenytoin contained cocaine, nicotine, phenobarbital, and phenytoin (Table). This and all subsequent urine specimens were negative for opiates, amphetamines, benzodiazepines, alcohol, propoxyphene, marijuana, and phencyclidine. Electroencephalography performed at 2 days of age revealed frequent focal sharp waves in the left central parietal areas and rarely in the right temporal area, without concurrent clinical seizure activity.

The infant initially required phenobarbital 25 mg/kg intravenously and phenytoin 10 mg/kg intravenously to control the right-sided seizure activity. After appropriate cultures were obtained, he was given ampicillin and gentamicin until culture results were available. Blood, urine, and cerebrospinal fluid cultures were negative, and antibiotic therapy was discontinued after 48 hours of age. The infant's blood pressure was extremely labile during the first 24 hours after admission to the high-risk nursery, with systolic levels ranging from 60 to 140 mm Hg. After 48 hours of age, his blood pressure returned to normal without therapy. The infant was given nothing by mouth until the seizures had been controlled for 48 hours. At that time enteral feedings were restarted, and maintenance oral phenobarbital therapy was begun. He remained seizure free with a dosage of 3 mg/kg/day with a serum level of 25.9 μ g/ml.

A repeat noncontrast CT scan performed at 7 days of age showed persistence of the left-sided infarct and increased gyral density in the region of the previously described infarct (Figure). A pneumogram made before discharge showed a normal respiratory pattern. Serial urine evaluations for cocaine metabolites showed persistence of benzoylecgonine until the infant was 4 days of age (Table). At 1 week of age, his neurologic status was markedly improved, but a mild right-sided hemiparesis persisted. Auditory screening using behavioral assessment of responses to a high-frequency (3000 Hz) warble tone of 80 and 90 dBHL revealed no evidence for a severe degree of bilateral hearing loss. On the Brazeltone Neonatal Behavioral Assessment Scale at 1 week, the infant's interactive capabilities and state organization were normal for age, but his psychomotor functioning was abnormal as a result of his hemiparesis. A repeat EEG at 2 weeks of age, while he was receiving phenobarbital, was normal in wake and sleep. Follow-up noncontrast CT scan at 2½ months of age showed a persistent area of focal encephalomalacia at the site of the previously noted acute infarct (Figure). Physical examination of the infant at 3 months showed increased deep tendon reflexes in the right biceps and brachioradialis without any other gross asymmetries. He also had persistent mild truncal hypotonia. To date, the baby has had no recurrence of seizures, and phenobarbital has been discontinued. His head circumference had fallen from the 50th percentile at birth to the 5th percentile at 3 months. He was otherwise an alert, sociable infant.

DISCUSSION

Cocaine acts centrally in the nervous system as a stimulant and peripherally as an inhibitor of nerve conduction. Reuptake of norepinephrine at the nerve terminals is

blocked, producing increased norepinephrine levels with subsequent vasoconstriction, tachycardia, and a concomitant acute rise in blood pressure.¹⁻³ Deaths in young adults after cocaine use have been attributed to myocardial infarction and cerebrovascular accidents.⁴⁻⁶ With the large ingestion of cocaine by the pregnant women in the present case, and the subsequent finding of cocaine in the urine of the infant, it appears that the fetal tachycardia and postnatal tachycardia and hypertension were the result of the in utero exposure of the fetus to cocaine. The CT scan of the neonate at 24 hours of age confirmed the presence of an acute focal cerebral infarction.

Possible causes for this infant's cerebral infarction include: thromboembolism (unproved because the placenta was not examined pathologically but was grossly normal in the delivery room), hypotension and bradycardia with cerebral hypoperfusion (initial Apgar score was 1, given for heart rate), and intrauterine and postnatal hypertension and subsequent cerebral hemorrhage (the spinal fluid obtained at 21 hours of age did show 1800 red blood cells without xanthochromia). The initial CT scan showed a wedge-shaped hypodense area in the distribution of the left middle cerebral artery. The follow-up scan at 7 days of age showed gyral hyperdensity in the region of the previous infarct. Diagnostic possibilities for the findings on this second scan included localized subarachnoid hemorrhage, parenchymal hemorrhage, or possibly parenchymal calcification. Because the third CT scan at 2½ months of age showed no residual hyperdensities, calcification is unlikely. Thus, the focal encephalomalacia seen in the third scan most likely resulted from either a bland infarct, a hemorrhagic infarction, or a small focal parenchymal hemorrhage. As in recently reported series of patients with neonatal cerebrovascular accident,⁷⁻⁹ our patient's infarction may have been caused by either intrauterine and postnatal hypertension and subsequent cerebral hemorrhage, or by peripartum hypotension and bradycardia with subsequent cerebral hypoperfusion. In subsequent patients with neonatal cerebrovascular accidents, relatively noninvasive diagnostic tests such as digital intravenous angiography may shed light on the anatomic site of pathologic conditions in patients such as ours. The exact timing of the cerebral infarction is not possible to define in the present case, but prenatal occurrence is likely, given the neonate's right-sided upper extremity weakness noted at birth.

Cocaine and its metabolites persist in the urine of an adult for up to 27 hours after intranasal use.¹⁰ The persistence of benzoylecgonine, a primary metabolite of cocaine, in the neonate's urine for 4 days is evidence for slow metabolism of cocaine by the neonate, probably related to the immaturity or relative deficiency of plasma cholinesterases in the newborn infant.

Drugs of maternal abuse previously investigated by our

group¹¹⁻¹³ have not produced persistent changes in the heart rate or blood pressure of neonates. Preliminary data from 23 pregnancies complicated by maternal cocaine use revealed an increased incidence of spontaneous abortions and abruptio placentae, as well as impairment of neonatal interactive and state organization abilities on the Brazelton Neonatal Behavioral Assessment Scale.¹⁴ Maternal cocaine use also may place the fetus at risk for tachycardia and hypertension, and thus for a cerebrovascular accident. Maternal cocaine use should therefore be considered in the differential diagnosis of neonates with perinatal cerebral infarction.

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Neurodevelopmental outcome after neonatal cerebrovascular accident

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Recent reports have documented that focal cerebrovascular accidents occur in the neonatal period¹⁻¹¹ and can be detected through the use of brain imaging techniques such as computerized tomography and cranial ultrasound. To our knowledge, there have been no reports of long-term follow-up of patients with neonatal CVA. Thus, it is difficult to discuss possible prognostic implications of such an event with parents.

We have identified 10 infants with documented CVA in the neonatal period, and this article describes long-term follow-up in the nine survivors.

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METHODS

Ten infants (Table) were identified as having incurred a focal CVA in the neonatal period on the basis of CT scans of the head. Five of these were previously reported.⁵ All but one of these infants were term, and all but the premature

See related article, p. 456.

CVA	Cerebrovascular accident
CT	Computed tomography
IVH	Intraventricular hemorrhage

infant developed focal motor seizures within 24 hours of life. The premature infant had recurrent apneic spells. These problems prompted performance of cranial CT scans, which demonstrated a focal area of lucency in a vascular distribution in each case. Eight of the 10 lesions were in the left hemisphere. None of the infants had