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Neurosonographic Abnormalities Associated with Maternal History of Cocaine Use in Neonates of Appropriate Size for Their Gestational Age

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PURPOSE: To determine whether increased incidence of neurosonographic abnormalities (predominantly of the basal ganglia and thalamus) in cocaine-exposed neonates who are small for their gestational age is attributable to the cocaine or to neonatal size. **METHODS:** Neonates whose sizes were appropriate for their gestational age with no evidence of hypoxia or respiratory distress were identified prospectively by a maternal history of cocaine use. Scans were performed within 72 hours of birth using a 7.5-MHz transducer following a standard protocol. The images were analyzed without access to patient information. Forty study neonates were compared with 34 control subjects who were appropriate in size for their gestational age, scanned using the same protocol. Comparisons were made using Fisher Exact Test, *t* test, and logistic regression. **RESULTS:** No control infant had neurosonographic abnormalities. In the study group, gestational age ranged from 27 to 41 weeks. Of the 40 study neonates, 14 (35%) had one neurosonographic abnormality; two had two abnormalities. The predominant lesion was focal echolucencies, mainly in the area of the basal ganglia (10 of 40, 25%). Other findings were caudate echogenicity (3 of 40, 7.5%), ventricular dilation (2 of 40, 5%) and one "moth-eaten" appearance of the thalamus. Lesions were more likely approaching term and were not related to prematurity or alcohol use. **CONCLUSION:** Apparently normal neonates with a maternal history of cocaine use are likely to have degenerative changes or focal infarctions in their basal ganglia attributable to cocaine. Neurosonography should be used to evaluate these neonates. The long-term significance of these lesions needs further evaluation.

Index terms: Infants, newborn; Ultrasound, in infants and children; Cocaine

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We (Dogra VS et al, Abnormal Neurosonographic Findings Associated with Maternal History of Cocaine Use in Appropriate-for-Gestational-Age Neonates, presented at the 31st Annual Meeting of the American Society of Neuroradiology, Vancouver, 1993) and others (1, 2) have found an increased incidence of echolucencies of the basal ganglia in neonates who are small for their gestational age and have been exposed to cocaine. In 1988 about 11% of the US population were regular cocaine users. About 6% of these used cocaine during pregnancy (3). Cocaine use during pregnancy adversely affects the development of the fetus (4). Are the echolucencies observed in neonates who are small for their gestational age attributable to cocaine use or to size of the neonates? To resolve this question we studied the neurosonographic abnormalities found in neonates of size appropriate for their gestational age with a maternal history of cocaine use.

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Materials and Methods

From August 1992 through December 1992, we prospectively identified 42 consecutive neonates of size appropriate for their gestational age with prenatal care and with

TABLE 1: Abnormal neurosonographic findings associated with maternal history of cocaine use in neonates appropriate for their gestational age

Category	Cocaine metabolites		Total	Significance versus Control Group
	Absent	Present		
Number	10	30	40	
Normal	6	20	26	
Abnormal	4	10	14[a]	$P < .001$
Focal echolucencies	2	8	10	$P < .002$
Caudate echogenicity	1	2	3	$P < .24$
Ventricular dilation	2	0	2	Not significant
"Moth-eaten" appearance of thalamus	0	1	1	Not significant

Note: P value by Fisher Exact Test.

[a] Two had two abnormalities.

no evidence of hypoxia or respiratory distress at birth, who were born in our institution to women with a history of cocaine use.

Gestational ages were assigned using the New Ballard Score, a maturational assessment of the gestational age based on neuromuscular and physical maturity (5), expanded to include extremely premature infants. Size appropriate for gestation age was defined as weight, head circumference, and length all within the 10th to 90th percentile range using Lubchenco norms (6). Neonatal urine toxicology by immunoassay was performed for the metabolites of cocaine, marijuana, opiates, and phencyclidine within 48 hours of birth. All positive specimens were confirmed by thin layer chromatography (7). Umbilical arterial and venous pH and pCO_2 were normal at birth. Apgar score at five minutes was seven or greater.

Real-time sonography was performed within 72 hours of birth, with a 7.5-MHz sector transducer, through the anterior fontanelle at a constant scan depth of 100 mm and constant gain settings. Six coronal (two anterior, two mid, and two posterior), two sagittal, and 10 parasagittal views (five each to right and left) were recorded.

The maternal history of alcohol use was recorded. All neonates in the study group had prenatal care with a minimum of six visits. The urine results were not known to the neurosonographer. The images were analyzed without access to information on patient status. The studies were interpreted twice by the same observers and scored as positive when the second interpretation concurred with the first. This study group was compared with a control group of neonates of size appropriate for their gestational age who had no maternal history of cocaine use who otherwise met study criteria and who had negative urine screening for cocaine metabolites, using Fisher Exact Test, logistic regression, and unpaired t tests.

Results

In the study group of 42, two were excluded. One was not of a size appropriate for gestational age on review, and one had no urine toxicology results. The remaining 40 of the study group were compared with the 34 control subjects appropriate for gestational age whose urine toxicology for cocaine metabolites returned negative.

Infants included in the study ranged from 27 weeks to 41 weeks of age. In the study group, mean head circumference was 32.1 ± 2.1 cm (mean ± SD, range 24.5 to 37 cm); mean gestational age was 37.6 ± 3 weeks (range 27 to 41 weeks), and mean birth weight was 2643 ± 594 g (range 940 to 3780 g). Seventy-five percent (30 of 40) of the subjects were positive for cocaine metabolites, and a positive history of alcohol use was obtained from the mothers of 19 of the 40 subjects. None of the 34 control subjects was positive for maternal history of cocaine or cocaine metabolites by design. No other drugs tested were detected in either group.

No control infant had a neurosonographic abnormality. Thirty-five percent of the study group (14 of 40, $P < .001$) had neurosonographic abnormalities. Neurosonographic findings are summarized in Table 1. Twenty-five percent of the study group (10 of 40, $P < .01$) had focal echolucencies measuring 2 to 4 mm in size and without evidence of hemorrhage. These were often multiple and distributed in the caudate, periventricular (inferolateral to the body of the lateral ventricle), and choroidal regions of the brain (Figs 1A and 1B).

Three of 40 in the study group (7%, $P = .23$) had caudate echogenicity in the area of the head of the caudate nucleus. This echogenicity did not change in echo texture on three follow-up scans, up to 40 days of life. All but one were bilaterally symmetrical (Figs 2A and 2B). Five percent (2 of 40) of the neonates showed mild ventricular dilation. In one case, the thalamus was variable in echotexture with multiple small hypoechogenici-

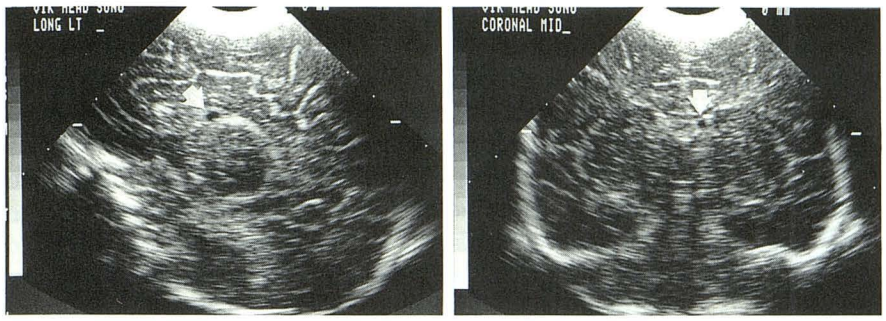

Fig. 1. *A*, Left parasagittal section showing a focal echolucency in the region of the caudate (*arrowhead*).

B, Coronal section corresponding to A.

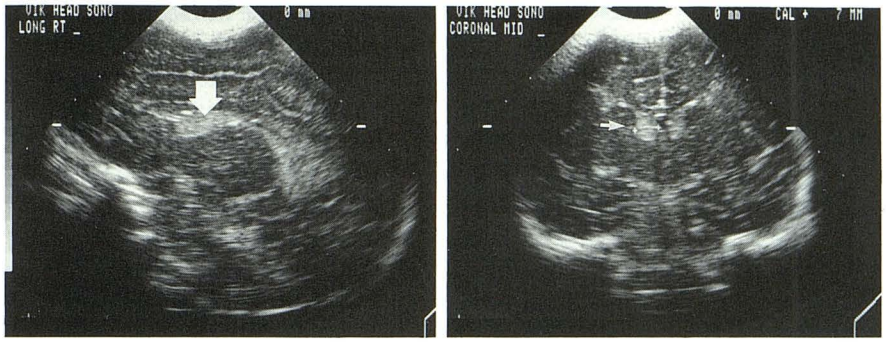

Fig. 2. *A*, Right parasagittal section showing echogenicity of the caudate (*arrow*).

B, Coronal section corresponding to A (*arrowhead* pointing to caudate).

ties and hyperechogenicities with blurred margins (Figs 3A and 3B), a "moth-eaten" appearance.

In the study group of 40 neonates of size appropriate for their gestational age, 11 were preterm and 29 were term infants. The mean age of the neonates with normal scans was less than the mean age of those whose scans were abnormal ($P < .05$). A neurosonographic abnormality was more likely at term. Distribution of neurosonographic abnormalities in relation to gestational age is given in Table 2. The likelihood of a lesion was somewhat reduced with prematurity ($P = .15$) and unrelated to history of alcohol use ($P = .81$), but these two were positively related to each other (9 of 11 preterm subjects versus 10 of 19 at term had alcohol history, $P < .06$, Fisher Exact Test).

Within the study group who all had a history of cocaine use, neurosonographic abnormalities were not associated with cocaine metabolites in the urine ($P = .71$).

Discussion

Cocaine is the most potent naturally occurring central nervous system stimulant, sharing many pharmacologic and adverse effects with synthetic stimulants such as amphetamines and phenmetrazine (8). More than 100 000 babies born in the United States annually are believed to have been exposed to cocaine or other drugs during the critical period of fetal brain development (9). The immediate perinatal effects can be abruptio placentae, prematurity, microcephaly, and symmetrical growth retardation.

Of potentially greater long-term significance are the neurodevelopmental problems of cognitive, emotional, and social development found in infants exposed to cocaine in utero (10), which become more apparent later in infancy (11). To identify the structural effects of cocaine that are attributable directly to cocaine exposure and not to its indirect effects on fetal growth we examined a cohort of infants who were of size appropriate for their gestational age with cocaine exposure but without perinatal and neonatal complications. This baseline structural data will be helpful in correlating neurodevelopmental abnormalities observed with structural lesions of the brain.

Focal echolucencies of the basal ganglia and choroid, caudate echogenicity, ventricular dilation, and a moth-eaten appearance of the thalamus associated with a maternal history of cocaine use were the findings in this study. The echogenicity of the caudate nucleus and hypoechogenicities and hyperechogenicities of the thalamus in

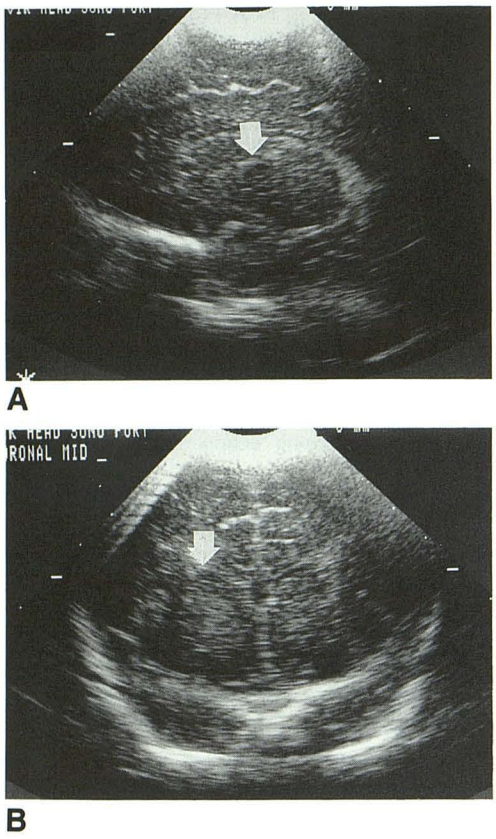

Fig. 3. *A*, Parasagittal section showing thalamus with multiple small hypoechogenicities and hyperechogenicities with blurred margins (moth-eaten appearance, *arrow*).

B, Coronal section corresponding to A.

TABLE 2: Distribution of neurosonographic lesions in relation to gestational age

Category	Term (>37 weeks)	Preterm (<37 weeks)
Number	29	11
Abnormal	12[a]	2[a]
Focal echolucencies	9	1
Caudate echogenicity	2	1
Ventricular dilation	1	1
"Moth-eaten" appearance of thalamus	1	0

[a] One in each group with two abnormalities.

our series are consistent with those shown by others in primates and humans in association with various forms of asphyxia (12–16). There is one case of moth-eaten appearance of the thalamus in our present series and three cases in our study of infants who are small for their gestational age. The normal thalamus has medium echoes; normal variation could have given this appearance, despite the control of technique, depth, and gain. We sought histopathologic correlation of this observation by reviewing 157 neonatal autopsies done at our center in the past 5 years and identified nine reports mentioning a maternal history of cocaine use. One of these reported a specific thalamic lesion on autopsy. It showed aggregates of microcalcification, neuronal degeneration, and edema (Fig 4). Microcalcifications were not present in other parts of the brain. Ultrasound findings before death were reported to suggest thalamic hemorrhage. The moth-eaten sonographic appearance may correspond to these pathologic changes. The thalamus has the second highest uptake of cocaine in the brain (17) and a high metabolic rate, which may make this structure more susceptible to the actions of cocaine.

Focal echolucencies were the predominant findings in the study group. It is important to distinguish these echolucencies from other cystic lesions in the brain. To differentiate them from periventricular leukomalacia and porencephalic cysts we have called them *focal echolucencies*. Periventricular leukomalacia and the focal echolucencies we observed are parts of the spectrum of hypoxic-ischemic encephalopathy but are essentially different from each other. Periventricular leukomalacia has been mainly described in relation to immaturity and acute perinatal distress (18) and refers to predominant involvement of white matter. Various morphologic forms of it have been described (19). In our study the echolucencies and echogenicities were not related to prematurity and were mainly of the gray matter of the caudate nucleus and area of the basal ganglia. None of the neonates had evidence of intrapartum asphyxia, as measured by umbilical pCO_2 and Apgar score. The location of lesions observed corresponds to the patterns of status

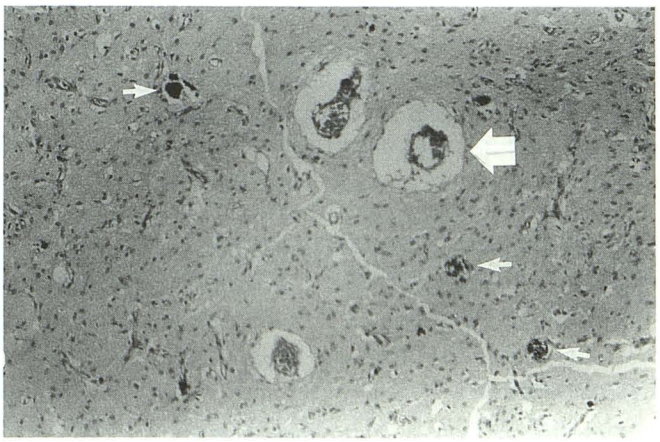

Fig. 4. Low-power microphotograph of thalamus showing foci of microcalcifications (*small arrows*) and perivascular edema (*large arrow*) in a neonate born to a cocaine-using mother.

marmoratus associated with chronic partial anoxia as shown by Myers et al (20–22) in primates and Volpe in humans (23). This could be related to the binge pattern of cocaine use. Porencephalic cysts are associated with intraparenchymal hemorrhage; we found no evidence of hemorrhage in any of these lesions.

The particular distribution of cerebrovascular lesions observed in our study seems to be related to the state of maturation of the cerebral vessels and the resulting responsiveness to placentally transferred cocaine (2). Furthermore, these lesions correspond to the patterns of ^{11}C-labeled cocaine uptake shown by Fowler et al in a positron emission tomography study of healthy adult volunteers (17), which was maximal in the corpus striatum, then the thalamus. The neurosonographic abnormalities found probably represent ischemic changes secondary to cocaine-induced vasospasm or hypoxic changes from maternal placental vasoconstriction.

The neurosonographic appearance of 26 neonates with a maternal history of cocaine use is normal either because of low sensitivity of this technique in detecting subtle lesions or, more likely, because of variations in fetal response, dosage, duration, maternal hemodynamic effects, or timing of exposure to cocaine. The lack of difference in lesions found between those with and those without cocaine metabolites within the study group indicates these lesions antedate delivery by an uncertain time period. The urine cocaine metabolite results in neonates are positive only in cases with maternal cocaine use within approximately 7 days before delivery (7).

Neurosonographic lesions have been reported by Dixon and Bejar in 28 cocaine-exposed infants. Unlike our subjects, 39% of their study group showed hemorrhagic cerebral infarcts by ultrasound at birth (1). This study confirms the echolucencies and ventricular dilation found in theirs, but we did not find the ventricular hemorrhages they reported, and our findings of caudate echogenicity and moth-eaten appearance of the thalamus, to our knowledge, are new. Our selection criteria for this appropriate-for-gestational-age series, based on maternal history of cocaine use, differs from the small-for-gestational-age series (Dogra VS et al, Abnormal Neurosonographic Findings Associated with Maternal History of Cocaine Use in Appropriate-for-Gestational-Age Neonates, presented at the 31st Annual Meeting of the American Society of Neuroradiology, Vancouver, May 1993), which was based on cocaine metabolite detection in the urine. The findings are qualitatively identical but lower in incidence. Schellinger et al have shown that echoencephalography is more sensitive than computed tomography (CT) for detection of small cystic lesions in neonates (24). The one infant in our study evaluated by CT confirms this. The echolucency shown in Figures 1A and 1B was not seen on CT scan.

Of two magnetic resonance (MR) studies of infants exposed to cocaine, that of Link et al (25) and that of Bandstra et al (Abnormal Neurosonographic Findings Associated with Maternal History of Cocaine Use in Appropriate-for-Gestational-Age Neonates, presented at the 31st Annual Meeting of the American Society of Neuroradiology, Vancouver, May 1993), neither found lesions in the brain with cocaine exposure. The first study had a small number of subjects (only nine with MR), and the median age of the neonate at MR was 3.6 months. It is likely that small cystic lesions could have healed by gliosis and would be impossible to detect at this age. The MR study of Bandstra et al showed an increase of the subarachnoid space in six of 21 neonates with cocaine exposure and reported no other central nervous system abnormality. We did not find a case of enlarged subarachnoid space except two with ventricular dilation. The enlargement of the subarachnoid space makes us wonder what structures have been diminished to create this space. Ultrasound is not the modality of choice to visualize the subarachnoid space, so we may have missed this finding. A prospective contemporaneous study of MR and neurosonography in the same cocaine-exposed neonates will be helpful in explaining these differences.

A frequent problem of studies attempting to identify the effects of cocaine is the potential confounding with effects of malnutrition, alcohol, and other drugs. In this series infants were in the appropriate growth range by standard norms (as a part of selection criteria). It is impossible to control strictly for malnutrition, because cocaine affects appetite. Control for maternal history of alcohol use did not alter the results. No other drugs were used by history or drug screening. Limitations of the present study are the lack of evaluation by other modalities, lack of a weight-matched control group, lack of a concurrent blinded study of intraobserver and interobserver variation, and absence of formal neurologic or neurobehavioral evaluation and follow-up of these apparently normal neonates.

Strengths of the study are the clear uniform selection criteria, consecutive examination of an entire cohort of infants meeting these criteria, standardized examination technique applied by a single sonographer in all cases, and review and confirmation of all positive and negative findings using a uniform classification system based on prior experience. This permits an estimation of the true incidence of lesions in this population. Neurosonography is the most operator dependent of all the neuroimaging modalities. We believe that correct identification of neonatal brain lesions requires standardization of sonographic technique used (depth and gain settings) and images obtained. This will prevent variability of settings and anatomy shown from interfering with sonographic interpretations.

Neurosonographic abnormalities were observed in 35% of the neonates of size appropriate for their gestational age in the control group with maternal history of cocaine use. The most common lesion was focal echolucency in the area of the basal ganglia, followed by caudate echogenicity, ventricular dilation, and thalamic heterogenicity. These lesions were more likely in term neonates ($P < .05$). They probably represent small infarctions of the structures involved, but the clinical significance of these findings needs to be defined. These findings will be helpful in studying the neuroanatomic correlates in the follow-up of cocaine-exposed infants. Apparently normal neonates of size appropriate for their gestational age born to mothers with a history of cocaine use have a high incidence of neurosonographic abnormalities attributable to cocaine. This study justifies routine neurosonographic evaluation of neonates with cocaine exposure.

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