ORIGINAL COMMUNICATIONS

AUTISM AND DEVELOPMENTAL ABNORMALITIES IN CHILDREN WITH PERINATAL COCAINE EXPOSURE

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Cocaine in all forms is the number one illicit drug of choice among pregnant women. Records of 70 children with cocaine exposure in utero who were referred for developmental evaluation at a large inner-city hospital were reviewed in an effort to determine whether a specific pattern of abnormalities could be discerned.

Patients received physical examinations, neurological screenings, and behavioral and developmental assessments based on the Gesell Developmental Inventory, and the Denver Developmental Screening Test. Documentation of specified drug use was obtained by history. Mean age (SEM) at referral was 19.2 (1.7) months.

All mothers used cocaine in one of its forms, although polydrug use was common. Growth parameters were low (median = 15th percentile). Significant neurodevelopmental abnormalities were observed, including language delay in 94% of the children and an extremely high frequency of autism (11.4%). The high rate of autistic disorders not known to occur in children exposed to alcohol or opiates alone suggests specific cocaine effects. (*J Natl Med Assoc.* 1992;84:315-319.)

Key words • cocaine • perinatal • autism • developmental abnormalities

Cocaine is the number one illicit drug of choice among pregnant women in the United States. New York City registered a staggering twentyfold increase in maternal cocaine use during the past decade.[1] A recent study by the National Association for Perinatal Addiction Research and Education (NAPARE) of 36 hospitals from around the country showed an overall 11% incidence of substance abuse in pregnancy (range: 0.4% to 27%).[2] While some effects may be present at birth, others may not be appreciated until years later.

Cocaine abuse in pregnancy in New York City first overtook opiate abuse in 1984 with 4.3 per 1000 newborns having positive cocaine exposure as reported on birth certificates to the Department of Health.[1] Subsequently, in New York City, the rate of abuse has continued to increase, with 21.1 per 1000 newborns reported as having positive cocaine exposure in 1988.[1] As these children approach kindergarten and first grade, there continues to be an explosion of reports in the media about the lack of preparedness of school systems to cope with the specific developmental and behavioral abnormalities of these cocaine-exposed children. Few long-term follow-up studies document the nature of

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TABLE 1. CHARACTERISTICS OF CHILDREN EXPOSED TO COCAINE IN UTERO

	No. (%)
Guardianship*	
Mother	16 (23)
Father	3 (4)
Grandparents	27 (39)
Aunts/uncles	7 (10)
Nonrelated foster parent	14 (20)
Agencies	3 (4)
Never lived with mother	32 (46)
Maternal Age†	
15 to 19 years	1 (1.8)
20 to 24 years	20 (36.4)
25 to 29 years	16 (29.1)
30 to 34 years	10 (18.2)
35 to 39 years	7 (12.7)
45 to 49 years	1 (1.8)
Mean	27.1 years
Maternal Drug Use*	
Cocaine	70 (100)
Alcohol	33 (47)
Opioids	10 (14)
Other‡	12 (17)
Age at Evaluation*	
0 to 6 months	14 (20)
6 months to 1 year	14 (20)
1 to 2 years	19 (27.1)
2 to 3 years	18 (25.7)
>3 years	5 (7.1)
Mean	19.2 months

*N = 70.
†N = 55.
‡Other = PCP and marijuana.

these abnormalities despite the reports of parents, foster parents, and workers in preschool programs. To characterize the pattern of abnormalities seen, this study reviewed the cases of 70 cocaine-exposed children referred to a developmental clinic for evaluation.

METHOD

A retrospective chart review of the behavioral and developmental assessments of all children with cocaine exposure in utero (N = 70) referred to the Harlem Hospital Developmental Clinic for evaluation and services between January 1, 1987 and December 31, 1989 was undertaken. Perinatal drug exposure was confirmed with a positive toxicology report in the child's medical chart, the mother's admission, or the referring physician's or agency's report. In most instances, the frequency of use or the time of use of a particular drug of abuse during gestation was unspecified. The maternal charts were unavailable for review.

All children were evaluated according to the clinic's routine screening procedure, and included a physical examination, neurological screening, and developmental assessment using the Denver Developmental Screening Test and items from the Gesell Developmental Inventory. Children were observed during a period of semistructured play with toy items consisting of soft animals, dolls, baby bottles, cars, trucks, and balls.

Children were brought to the clinic by their current caretaker, who was allowed to remain in the room as a silent bystander. Growth data were analyzed using the Centers for Disease Control's anthropometric statistical package (CASP) derived from the NCHS/CDC reference population.[3] Group differences were analyzed with the Student's *t* test using the BMDP statistical package.[4]

RESULTS

Characteristics of the study population are shown in Table 1. Less than 25% of the children were in the care of their biological mothers. Grandparents were most often the primary caretakers of the children. At the time of referral, there were five children who had been placed in two homes, the maximum number of home placements.

The mean age of the mothers in the study sample was 27.1 years. Slightly more than 30% of the mothers were 30 years or older at the time of delivery (Table 1). The distribution was similar to that of the general population of mothers delivering at Harlem Hospital with the exception that few adolescents were represented in the study population (1.8% versus 13.9%).

Although documentation of total drug use occurred in some cases by history alone, polydrug use appeared common (Table 1). Information concerning maternal cigarette smoking was not available.

The patients were referred at ages ranging from 1 month to 5 years (Table 1). Males represented 60% of the population. Mean birthweight was 2250 g with only 42% of the infants weighing ≥2500 g. Mean birthweight of full-term infants was 2808 g. In comparison, 86% of the infants in the general population born at the hospital weighed ≥2500 g. Mean gestational age (SEM) determined by reports from referring physicians and agencies was 36.4 (0.7) weeks, with 44% representing preterm deliveries.

Perinatal polydrug-exposed children had a mean (SEM) height/age percentile (HAP) of 31.5 (4.2) and a

TABLE 2. DISTRIBUTION OF HEAD CIRCUMFERENCE PERCENTILES

Percentile	No. (%)
<5th	24 (34.3)
5th to 25th	24 (34.3)
25th to 95th	21 (30)
>95th	1 (1.4)

mean (SEM) weight/age percentile (WAP) of 30 (3.9), in comparison to children admitted to the institution for failure to thrive, who had an HAP of 9.9 (2.2; $P<.0001$) and a WAP of 6.5 (1.6; $P<.0001$). Despite the relatively normal mean percentiles of perinatal polydrug exposed infants, both the median HAP and WAP equaled 15, indicating an excessive number of small children in this population. The head circumference data (Table 2) showed 34% of the subjects had head circumferences below the 5th percentile at the time of referral.

Significant developmental delays were noted in all areas tested (Figure). While most of the subjects with language delays had difficulties with expressive skills, more than 11% had severe communicative disorders in which receptive as well as expressive skills were abnormal. Abnormalities in language skills were evidenced by failure to vocalize other than cry until 3 or 4 months, delayed acquisition of words, limited use of newly learned words, failure to call the primary caretaker mama/dada or by name until well after 15 months of age, or failure to combine two different words in a phrase by 2½ years. In some children, the language abnormality took the form of long periods of silence. Pointing was frequent. The subjects diagnosed as autistic were essentially nonverbal except for the occasional parroting of complete sentences without communicative intent.

Characteristic fine motor delays included failure to bring hands to the midline, to engage in midline hand play, or to exchange items from one hand to the next at the age-appropriate time. Evidence of visual motor disturbances and difficulties in copying straight lines, circles, or more complex forms were evident in some children. Drawing a person represented a major difficulty for all children 4 years and older.

Gross motor delays were seen primarily in conjunction with hypertonicity and premature delivery. The most common abnormalities included the failure to sit or walk by the age-expected norm. Spastic diplegia, often seen in these instances, continued well into the second year of life in some children, while in others it

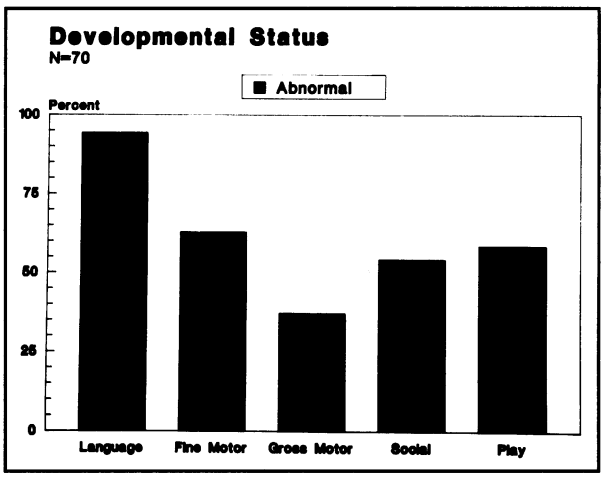

Figure. Distribution of neurodevelopmental abnormalities seen in children exposed to perinatal polydrug exposure in utero.

spontaneously resolved. A small number of children evidenced precocious motor development associated with mild hypertonicity or hyperactivity.

Delays in personal social skills often resulted from abnormalities in other areas. Language-delayed children cried to make their wants known. Children with motor difficulties were unable to dress, undress, or feed themselves by the appropriate age. Children who were markedly disorganized, appeared cognitively impaired, or were diagnosed as autistic failed to engage in appropriate interactive activities. In addition, explosive behavior, lability of affect, indiscriminate attachment to strangers, and persistent refusal to comply with simple commands were common abnormalities noted. The absence of standardized measures for these behavioral abnormalities precluded quantification of the extent and severity of the disorders.

There was generally a paucity of symbolic play. Dolls were often examined in a detached manner, dismembered, or quickly discarded. Blocks were often thrown about the room. Toy cars and trucks were either mouthed or thrown on the table. In some cases, there was no interest in any of the toys presented, but rather interest in opening and closing drawers, banging doors, or playing with running water.

Detectable neurological abnormalities were seen in more than 40% of the children (Table 3). In the one deaf child, the workup revealed a partially absent corpus collosum and a partially developed cerebellum. One child was blind. Computerized tomography of the head of this child revealed bilateral well-healed symmetrical infarctions cutting across each optic tract. Hypertonia

TABLE 3. DISTRIBUTION OF NEUROLOGIC ABNORMALITIES

Abnormality	Frequency (%)
Hearing deficit	1 (1.4)
Visual deficit	3 (4.3)
Hypotonicity	1 (1.4)
Hypertonicity	21 (30)
Endocrinological	1 (1.4)
None	43 (61.4)

was present in 30%. One child had isolated growth hormone deficiency. At the time of evaluation, only one child had a seizure disorder.

Neurobehavioral abnormalities included hyperactivity and autistic disorder (Table 3) as defined by *Diagnostic and Statistical Manual of Mental Disorder (DSM-III-R)* criteria.[5] In many instances, hyperactivity was seen in conjunction with perseverance acts, such as running back and forth across the room, jumping up and down on a toy, climbing over and over again on a chair or examining table and then jumping off, or other seemingly nonpurposeful activities.

Eight (11%) of the children met *DSM-III-R* criteria for autism. Of these eight children, six were full-term and two were born at 32 to 34 weeks gestation. The mean age of their mothers at delivery was 23½ years. Three mothers had histories of alcohol use on a regular basis, and one had used phencyclidine. Only one mother reported the use of heroin.

DISCUSSION

To date, most reports on cocaine effects deal with the adult population. Recently, the scientific community has begun to document some of the specific adverse effects on the fetus and developing child. Growth retardation in cocaine-exposed infants at birth has been documented in numerous studies and is one of the least controversial adverse effects ascribed to the drug.[6-12] The data in this study, showing 50% of the children at or below the 15th percentile in height and weight, would suggest that this problem may extend beyond the newborn period.

Neurobehavioral and developmental problems are less well-studied. Chasnoff et al found a greater degree of tremulousness and startle response in cocaine-exposed newborns and lower scores on the Brazelton Neonatal Behavioral Assessment Scale for interactive behavior and state organization.[13] Oro and Dixon found altered neonatal behavior patterns, including abnormal sleep patterns, poor feeding, tremors, and hypertonia.[8] Abnormalities in play skills have been reported by Howard et al[14] and by numerous caretakers and preschool workers. A recent long-term study of behavior and development by Howard et al suggests more permanent disabilities involving disturbances in relatedness, affect regulations, language development, and attention span.[14]

Several reports have now been made on central nervous system abnormalities. Electroencephalographic (EEG) abnormalities were noted in almost 50% of a group of cocaine-exposed newborns at Beth Israel Hospital in New York City, but only one EEG remained abnormal at 12 months.[15] Infarctions, cystic areas, atrophy, and other structural abnormalities have also been noted and raise serious concerns about long-term effects.[16-18]

The 70 children included in this report demonstrated abnormal findings in most neurobehavioral and developmental areas at ages considerably beyond the newborn period. In addition, the most intriguing and perhaps most disturbing data relate to the presence of *DSM-III-R* criteria for autistic disorder in 11% of the children. Autistic disorder is a rare syndrome previously reported to occur in 2 to 21 per 1000 live births.[19] To our knowledge, autism has not previously been reported in association with in utero drug exposure.

Low socioeconomic status, lack of prenatal care, poor nutritional status, cigarette smoking, and the use of multiple psychoactive drugs may all have contributed to abnormal indices of growth and development in this population. In particular, alcohol abuse in association with cocaine abuse has been suggested as a combination potentiating adverse outcome.[20-22] In adults, increased heart rate and blood pressure have been described after combined ethanol and cocaine administration in excess of that seen when a similar dose of cocaine is administered alone.[22] Hepatotoxicity as evidenced by increased hepatic serum alanine aminotransferase activity has been demonstrated in mice with cocaine and ethanol combinations compared to either drug alone.[20] Finally, rats have been shown to have increased brain:serum cocaine ratios when cocaine and ethanol are taken together in comparison to a similar dose of cocaine alone.[21] In a retrospective analysis such as this study, these variables could not be examined.

Other potentially confounding variables may include the caretaker's ability to care for and interact with the child, as well as the extent to which the child had been shifted from one caretaker to another. Children in the study appeared to live with very caring and concerned caretakers. Several foster mothers expressed the desire

to adopt. Most (92%) of the children had only had one foster home placement at time of referral. Thus, home environment did not appear to be associated with the abnormalities seen in this study.

The data summarized here must be interpreted with caution. This is a retrospective review in which complete ascertainment of maternal drug use, eg, cigarette smoking, and duration of exposure is impossible. In addition, the drug abuse seen was clearly polydrug abuse, thus confounding the interpretation of cocaine as the responsible agent. The sample comes from referrals to a developmental specialist, and very likely encompassed the most affected and most difficult children. The range and severity of the pathology observed is likely to reflect a "worst-case" scenario, and the extent to which it is representative of cocaine-exposed children on the whole remains to be determined.

This retrospective review suggests a pattern of developmental abnormalities of grave concern to us as African-American investigators, since early identification of these children is critical for proper referral to needed services. The next step is the implementation of large-scale controlled prospective studies that include routine standardized follow-up assessments with respect to psychometrics, language skills, and play skills, as well as the ongoing assessment of the impact of the child's environment. Such prospective investigations are urgently needed in order to make inferences regarding the responsible agent for these abnormalities and to develop timely interventions.

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