ORIGINAL ARTICLE

Neurodevelopment of adopted children exposed in utero to cocaine: the Toronto Adoption Study

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Abstract

Background: Published studies of children's neurodevelopment after in utero exposure to cocaine have not separated intrauterine from postnatal environmental effects as cocaine-using mothers cluster in low socioeconomic classes and have other risk factors.
Methods: To overcome this limitation, a study was done to assess physical and neurodevelopmental characteristics of 52 children: 26 were adopted by parents who sought counselling in the Motherisk Program at the University of Toronto for prenatal cocaine exposure, and 26 were controls matched for maternal intelligence quotient (IQ), socioeconomic status and gestational age.
Main outcome measures: Head circumference, McCarthy General Cognitive Index (GCI) score, language performance and temperament tests.
Results: The children in the study group had smaller head circumferences (34th versus 54th percentiles p = 0.009), lower McCarthy GCI scores (102.8 versus 114.2, p = 0.02), poorer receptive and expressive language performance on the Reynell test, and higher activity levels, less persistence and increased distractibility on temperament tests. On multivariate analysis, cocaine exposure was significantly (p = 0.001) associated with lower IQ and poorer language development independent of intrauterine growth retardation and other potential confounders.
Interpretation: By controlling for postnatal environmental factors, this adoption study documents intrauterine developmental risks associated with cocaine exposure. Follow-up into school years is warranted to evaluate the extent of these effects.

Résumé

Contexte : Dans les études publiées sur le développement neurologique des enfants exposés à la cocaïne in utero, on n'a pas séparé les effets in utero des effets environnementaux postnataux, car les mères qui consomment de la cocaïne sont regroupées au bas de l'échelle socio-économique et présentent d'autres facteurs de risque.
Méthodes : Pour contrer cette limite, on a réalisé une étude afin d'évaluer les caractéristiques du développement physique et neurologique de 52 enfants : 26 ont été adoptés par des parents qui ont consulté le programme Motherisk à l'Université de Toronto parce que l'enfant avait été exposé à la cocaïne avant sa naissance, et 26 étaient des témoins jumelés en fonction du quotient intellectuel (QI) de la mère, de sa situation socio-économique et de l'âge de la grossesse.
Principales mesures de résultats : Circonférence du crâne, indice de cognition générale (ICG) de McCarthy, performance linguistique et résultats de tests de tempérament.
Résultats : Les enfants du groupe d'étude avaient le crâne plus petit (34^{e} percentile par rapport au 54^{e}, p =

0,009), des résultats ICG McCarthy plus faibles (102,8 contre 114,2, p = 0,02), une performance linguistique moins bonne sur le plan de la réception et de l'expression, indiquée par le test de Reynell; les tests de tempérament indiquaient des niveaux d'activité plus élevés, une persistance moindre et un penchant plus prononcé à se laisser distraire. L'analyse à variables multiples a révélé un lien important (p = 0,001) entre l'exposition à la cocaïne, un QI plus bas et un développement linguistique moins avancé, sans égard au retard de croissance intra-utérine et à d'autres facteurs possibles de confusion.

Interprétation : En contrôlant les facteurs environnementaux postnataux, cette étude sur l'adoption décrit les risques associés à l'exposition à la cocaïne pour le développement intra-utérin. Le suivi au cours des années scolaires est justifié pour évaluer l'ampleur de ces effets.

Introduction

A large number of children are exposed in utero to cocaine,[1] giving rise to serious concerns about their neurodevelopment and well-being. However, a large body of follow-up studies of infants and children with intrauterine cocaine exposure has not consistently substantiated poorer neurodevelopment.[1–19] A major difficulty in this research is the large number of confounders clustering in the families of these children, including poverty, single motherhood and unstable parenting.

In this study, we offer a unique experimental paradigm to assess the effects of in utero cocaine exposure more directly, by eliminating postnatal environmental confounding effects. We studied children exposed prenatally to cocaine who were adopted shortly after birth into middle-class families and compared them to controls matched for environmental background factors. To the best of our knowledge, this is the first study of its kind to use this experimental approach to show that, similar to results using animal models, cocaine is a powerful developmental neurotoxin.

Methods

Subjects

All families of adopted children referred between January 1989 and July 1997 to the Motherisk Program for adoption counselling were contacted for follow-up when the children were 30 months of age or older. Their biological mothers were known to have used cocaine throughout pregnancy. At the time of the initial visit to our program, none of the adoptive parents reported having perceived any physical or developmental abnormalities in the adopted children, and in no case were such problems the reason for the consultation. The use of cocaine by the biological mother was established by positive self-reports volunteered by the biological mother. All of the 26 families fulfilling these criteria agreed to participate in the study.

To obtain a control group, each adoptive mother was paired with the first woman in the Motherisk Program database who matched the adoptive mother with respect to socioeconomic status (SES) (within 5 points on the Hollingshead scale[20]), maternal intelligence quotient (IQ) (within 7 points on the Wechsler Adult Intelligence Scale [Revised] (WAIS-R),[21] and the child's gestational age. Premature infants were matched on gestational age (+ 2 weeks), and the age at testing. Matching for maternal IQ and socioeconomic class of the mother controlled for the 2 variables most strongly predicting the home environment of the child.[22] Because prematurity can be associated with slower or impaired neurodevelopment,[23] gestational age is an important factor to consider when measuring cognitive development in children. The matched control women attended the Motherisk Clinic during pregnancy for counselling after gestational exposure to nonteratogenic agents (e.g., penicillins, acetaminophen), and they and their children were tested according to the same protocols as the study families. None of them used drugs of abuse or alcohol during the index pregnancy. Three control mothers and 4 adopting mothers reported cigarette smoking.

Medical and background information

For each biological mother, the following data were extracted from the records of Children's Aid societies or pediatricians: age, medical and obstetric history, clinical diagnoses, time and duration of use of medicinal and recreational drugs, and alcohol and cigarette use during pregnancy. Details on the course of pregnancy, mode of delivery and pregnancy outcome were obtained through interviews with the women (control group) and from medical records (biological and control mothers). Information about the child's birth weight, gestational age, neonatal course and complications were recorded. Details of developmental milestones were obtained by interviewing the adoptive and control mothers during the neurobehavioural testing and from reports of the children's pediatricians. Also obtained were the duration of time spent with the biological mothers, the child's age at adoption and the number of foster homes in which the children prenatally exposed to cocaine resided before adoption. This information aimed to assess the level of stability in the child's environment during the first few postnatal years of life.

Tests and measures

Maternal IQ was assessed with the WAIS-R.[21] SES was assessed with the Hollingshead Scale.[20] Each child received a complete physical and neurologic examination by the same physician. The children were tested between 31 and 94 months of postnatal age.

All children were tested with the McCarthy Scales of Children's Abilities,[24] a widely used test of cognitive development for children in the age range of 30 months to 8.5 years. The McCarthy scales provide a global cognitive index (GCI) (mean [and standard deviation] = 100 [6]) and T scores (mean [and SD] = 50 [10]) for subscales of verbal, perceptual, quantitative, memory and motor abilities. Hence, a broad range of clinically meaningful cognitive abilities that may be predictive of subsequent learning disability is provided. Scores of the 20 individual subtests were converted to z scores (mean [and SD] = 0 [1]) based on norms for specific age groups. The McCarthy test has been used extensively in other studies of intrauterine exposure to toxins (lead, alcohol) and medicinal drugs (e.g., phenytoin).[22,25] The children's language abilities were assessed with the Reynell Developmental Language Scales,[26,27] which evaluates speech quality (notably articulation problems), output and language maturity. The Reynell test has also been used to test the effects in pregnancy of drugs and chemicals, including phenytoin and antiepileptic drugs.[22,25]

The parents completed the age-appropriate Carey temperament test on their children. This is a 100-item questionnaire that provides scores on 9 temperament scales as well as a global temperament rating.[28] This is a well-established measure for children aged 3 to 8 years. It consists of 100 age-appropriate descriptions, which parents score on a 6-point scale from "almost never" to "almost always." Items are scored for 9 domains of temperament, derived originally from factor analyses. The 9 scales include: activity, regularity of routines, approach/withdrawal, adaptability, intensity, mood, persistence, distractibility and threshold of response. Scores from individual scales are used to classify children into different temperament style subtypes (i.e., easy, difficult, slow-to-warm-up). The scores are standardized in a way that higher scores reflect more positive behaviour (e.g., less distractibility or more persistence). Scores on early temperament tests are reportedly stable and predictive of subsequent learning disabilities and behaviour problems. Parents also completed the Parenting Stress Inventory,[29] a 120-item questionnaire evaluating parent-perceived stress in child and parent domains.[28] Testing was performed in our laboratory by a team comprising pediatricians, a neurologist, a psychometrist and a neuropsychologist.

The psychometrist who performed the evaluation was blinded to the nature of maternal exposure and assignment of the mother–child pairs to the study or control group, as was the neuropsychologist who oversaw and supervised the assessment.

The protocol was approved by the Research Ethics Board of The Hospital for Sick Children. Consent was obtained from all adoptive and control mothers.

Statistical analysis

Data analysis proceeded in 2 steps: univariate analysis followed by multivariate analysis. For the temperament test, an exploratory factor analysis was used to reduce the number of behavioural variables. The suggested structures were further examined by the reliability procedure. Sample means were compared using the Student's t-test for independent samples. A p value less than 0.05 was considered significant.

Multivariate analysis served to explore the relationships between criterion variables differentiating the groups and several predictors simultaneously. Multiple linear regression models examined the influence of each predictor on the criterion while other predictors were held constant. The regression procedure presented statistics for the resulting equation (including R^2 and analysis of variance), regression coefficients and associated statistics for the predictors in the equation, and statistics for predictors being considered that were not in the equation.

Results

Table 1 presents data on the children's early and current physical development and on maternal characteristics. Cocaine-exposed children had a lower birth weight and, at the time of testing, were shorter and had smaller head circumferences than control children not exposed to cocaine. Six cocaine-exposed children had a head circumference more than 2 standard deviations below the mean. Gestational age did not differ significantly between the groups owing to our matching process.

Mothers in the control group were significantly younger than the adoptive mothers of the exposed group. In contrast, the mean (and SD) age of biological mothers was significantly younger (28.8 [4.7] v. 35.0 [4.1] and 40.5 [8.7]). Seven biological mothers reported drinking alcohol periodically. Although they were not alcohol dependent, more accurate information is not available. Adoptive mothers of exposed children did not differ from mothers of controls with respect to IQ or SES.

Table 2 provides the findings for neurodevelopmental scores and temperament. Cocaine-exposed children scored significantly lower than children not exposed to cocaine on the McCarthy GCI and Reynell receptive and expressive language scales. Four children in the study group had scores in the verbal comprehension more than 1 standard deviation below the mean compared with 2 children in the control group. Seven cocaine-exposed children had their expressive language scores more than 1 standard deviation below the mean versus 4 in control group.

For the temperament test, an exploratory factor analysis conducted on control group data only (24 children) identified 4 underlying factors. The first factor included intensity, threshold and distractibility scales and was considered to represent an arousal scale. The second factor, which included approach, adaptability and mood was thought to represent sociability. The third factor included activity and persistence and was thought to reflect hyperactivity, whereas the fourth factor behaved independently and contained only rhythmicity. Composite scores based on these 4 factors were computed for both groups of children, with higher scores signifying a more positive characteristic. Cocaine-exposed children differed from those not exposed to cocaine only on hyperactivity. The cocaine-exposed group scored

Table 1: Child and mother characteristics of children exposed (patient group) and not exposed (control group) to cocaine in utero

	Patient group		Control group				
Characteristics	No.	Mean (and SD)	No.	Mean (and SD)	*t* value	*df*	*p* value*
Children							
Birth weight, g	22	2571.8 (820.2)	26	3368.6 (705.6)	–3.62	46	0.001
Gestational age, wk	23	37.8 (3.4)	26	39.2 (2.0)	1.99	47	0.089
Child's age, mo†	26	56.8 (17.9)	26	47.0 (13.3)	2.23	50	0.03
Weight, percentile†	25	34.5 (32.3)	24	56.1 (29.1)	–1.39	47	0.171
Height, percentile†	25	44.6 (31.8)	25	64.5 (25.6)	–2.43	48	0.019
Head circumference, percentile†	25	34.5 (25.0)	25	53.9 (25.4)	–2.72	48	0.009
Mothers							
Maternal intelligence quotient	26	102.4 (12.1)	26	99.0 (12.1)	1.00	50	0.323
Socioeconomic status (Hollingshead scale)	26	47.6 (13.9)	26	46.2 (14.6)	0.34	50	0.735
Age, yr†	22	40.5 (8.7)	18	35.0 (4.1)	2.46	38	0.019

*2-tailed *t*-test
†At time of testing

lower, which meant that they were more hyperactive.

Regression analyses were conducted on the major test scores with the following as predictors: maternal IQ and SES, gestational age, birth weight, head circumference, group status (cocaine-exposure versus nonexposure), mother's drinking and mother's smoking. Table 3 shows the results that reached statistical significance. For McCarthy GCI and the Reynell receptive language scale, significant predictors were group status and maternal IQ. Children not exposed to cocaine and whose mothers had higher IQs obtained higher scores, with nearly 25% of the variability in cognitive functioning and 21% in receptive language being explained by these 2 variables. Group status appeared to be a stronger predictor of intellectual functioning than receptive language. Regarding expressive language, the results indicated group status, smoking during pregnancy and gestational age were significant predictors, accounting for more than 80% of the variability in expressive language. Better expressive language was observed if the child was not exposed to cocaine or cigarette smoking.

The regression analyses revealed significant results for 3 of the 4 temperament factors: arousal, hyperactivity and sociability. On the arousal scale, higher scores signifying lower arousal levels were predicted by a longer gestational age: that is, children born closer to term seemed to be less easily aroused. For hyperactivity, nearly 45% of the observed variability on this scale was explained by the combination of group status, maternal IQ and head circumference. Regarding sociability, mother's IQ was the strongest predictor followed by group status, which together accounted for 21% of the variance. Children of mothers with higher IQs and who were not exposed to cocaine in utero were seen as more outgoing, easier in adapting to new situations and happier.

Discussion

It has been estimated that in American inner cities up to 30% of pregnant women consume cocaine. However, even in other locations its use is wide; in Toronto, for example, we estimated that as many as 6.25% of fetuses are exposed to cocaine in late gestation, based on a positive hair test.[30]

By 1999, scores of longitudinal studies had examined the neurodevelopment of children after intrauterine exposure to cocaine.[1–19,31–34] Numerous studies have measured IQ in different cocaine-exposed age groups and matched control children with conflicting results.[9,16] Language development was assessed among cocaine-exposed children, and a detrimental effect of cocaine on language development was confirmed or refuted in several studies.[5,32] Various aspects of child behaviour were assessed by different studies, based on parents' or teachers' reports, showing or failing to show untoward effects.[9,11,31] More specifically, these studies measured a variety of end-points including impulsivity, distractibility,[4,9,11,19,31] problem behaviour in school, delinquency and aggressive behaviour.

Table 2: Neurodevelopmental achievements and temperament scores of children exposed (patient group) and not exposed (control group) to cocaine

	Patient group		Control group				
Characteristics	No.	Mean (and SD)	No.	Mean (and SD)	*t* value	*df*	*p* value*
McCarthy and Reynell scores							
Intelligence quotient (McCarthy GCI)	26	102.8 (11.1)	26	114.2 (14.3)	–3.22	50	0.002
Reynell — receptive	26	–0.04 (0.76)	26	0.45 (0.86)	2.46	38	0.019
Reynell — expressive	25	–0.52 (0.80)	26	0.04 (0.84)	–2.20	50	0.032
Temperament subscales scores							
Arousal	24	101.2 (8.1)	24	102.6 (8.4)	–0.63	46	0.533
Sociability	24	96.8 (16.7)	24	102.5 (10.2)	–1.44	46	0.158
Hyperactivity	24	86.4 (14.1)	24	101.6 (10.5)	–4.25	46	0.0001
Rhythmicity	24	88.8 (17.1)	24	93.1 (16.2)	–0.91	46	0.367

GCI = General Cognitive Index.
Reynell — receptive = Reynell, verbal comprehension.
Reynell — expressive = Reynell, expressive language.

The common denominator of these mostly meticulous and well-performed studies is that children exposed in utero to cocaine have been raised by their natural mothers. Thus, their risk of scoring lower than controls on standard neurobehavioural tests is substantially increased owing to confounders such as poverty, a disrupted family, psychiatric comorbidity and other postnatal factors.[7,15,32]

Different statistical methods have been used to control for such confounders, and, in general, these studies have not found cocaine by itself to be consistently associated with impaired cognitive development. It has been argued that cocaine may affect other areas of brain function resulting in more subtle changes,[14] including distractibility, temperament and other behaviour patterns. There are, however, methodologic problems inherent in previous study designs. If, for example, poverty and other environmental factors (e.g., disruptive care) are much stronger in their adverse effects than cocaine,[7,15,32] then it may not be possible to discern cocaine from such factors, rendering these longitudinal studies insensitive to some of the developmental effects of cocaine. Indeed, recent studies comparing cocaine-exposed children to poor children not exposed to cocaine in utero failed to show any differences in IQ.[10]

These findings in longitudinal studies are in sharp contrast to recently published animal experiments in which cocaine, at relatively low doses, caused measurable damage to specific neuronal populations.[26,35] To date, no study has directly evaluated neurohistologic changes in infants after intrauterine exposure to cocaine.

In this study we wished to explore an entirely different experimental paradigm in an effort to understand the potential effects of intrauterine exposure to cocaine. By recruiting children exposed in utero to cocaine and adopted by middle-class families, we wished to separate intrauterine effects of cocaine

Table 3: Multiple linear regression for predicting neurodevelopmental achievements and temperament in children

	Value				95% confidence interval	
Predictors/dependent variables	B	β	*t*	*p*	Lower	Upper
Child's IQ (McCarthy GCI)						
Group status	–12.50	–0.45	–3.63	0.001	–19.43	–5.58
Mother's IQ	0.31	0.28	2.24	0.029	0.03	0.59
Constant	83.30		5.96	0.000	55.20	111.40
Reynell — receptive						
Group status	–0.57	–0.35	–2.68	0.010	–1.00	–0.14
Mother's IQ	0.02	0.35	2.68	0.010	0.01	0.04
Constant	–1.84		–2.12	0.039	–3.58	–0.10
Reynell — expressive						
Group status	–1.77	–0.97	–7.66	0.000	–2.27	–1.28
Gestational age	–0.15	–0.65	–4.38	0.001	–0.23	–0.08
Cigarette smoking	–0.84	–0.46	–3.50	0.004	–1.36	–0.33
Constant	6.66		4.64	0.000	3.58	9.74
Temperament — arousal subscale						
Gestational age	0.89	0.30	2.08	0.043	0.03	1.76
Constant	67.40		4.06	0.000	33.92	100.88
Temperament — hyperactivity subscale						
Group status	–20.57	–0.71	–5.65	0.000	–27.92	–13.21
Mother's IQ	0.38	0.31	2.63	0.012	0.09	0.67
Head circumferance	–0.17	–0.31	–2.56	0.014	–0.30	–0.04
Constant	73.77		5.12	0.000	44.67	102.86
Temperament — sociability subscale						
Group status	–7.54	–0.27	–2.03	0.048	–15.03	–0.05
Mother's IQ	0.48	0.41	3.09	0.003	0.17	0.79
Constant	55.94		3.65	0.001	25.09	86.78

IQ = intelligence quotient, GCI = General Cognitive Index from those of the typically high-risk environmental determinants in these children. To the best of our knowledge, this is the first such study to explore the effects of cocaine in this way. A potential selection bias was avoided because none of the families examined by us perceived any developmental issues with their children at the time of the referrals.

In a preliminary report of this cohort,[5] children exposed in utero to cocaine achieved significantly lower scores than controls on both expressive and receptive language scales of the Reynell test, but they did not differ significantly in IQ. However, most of the children were younger than 3 years at the time of testing, and those tested after 30 months of age tended to score lower than their controls. By extending the study to include older children and to control for determinants such as intrauterine growth retardation and prematurity (which are more prevalent in cocaine-exposed newborns),[2,10] we aimed to overcome a potential type II error. In addition, we wished to assess child behaviour more extensively, including activity, temperament, adaptability and mood, because these domains may be more sensitive to the effects of cocaine than cognitive development.

We corroborated previous findings that at birth, infants exposed in utero to cocaine are of significantly lower length and weight. Because we did not have head size at birth, we cannot comment on that.

The adopting mothers were older than the controls. However, as they were of similar IQ and SES, it does not appear that family differences should affect child achievements. We cannot rule out that adopting families are more motivated to stimulate the children.

The present study shows that intrauterine exposure to cocaine affects overall intellectual functioning and, in particular, verbal skills. Numeracy abilities also appear to be somewhat vulnerable to the effects of cocaine exposure whereas visuospatial, visuomotor and visual memory abilities are largely unaffected (data not given). Temperamentally, the children tended to be more active than normal (which mothers often find very stressful) and were less persistent and more distractible. Interestingly, parents of cocaine-exposed children reported less stress in their personal lives than those of nonexposed children, further suggesting that this effect is primary and not caused by familial factors. Future studies should corroborate these findings with teachers' reports, which were not available to us.

Overall, these results suggest that cocaine exposure in utero leads to poorer language and verbal processing skills and may increase the risk of subsequent attention deficit hyperactivity disorder. These observations are consistent with recent animal studies in showing that cocaine damages dopaminergic and serotonergic neurons, which are known to modulate such behaviours.[36,37]

Our study suggests direct neurotoxicologic effects to be associated with cocaine, affecting IQ, and language development, and resulting in a higher prevalence of difficult temperament, less persistence and more distractibility. These deficits have serious potential to impact the development of children during school years.

Because women using cocaine throughout pregnancy almost invariably smoke cigarettes, consume alcohol and other drugs, it is impossible to relate the effects detected by us to cocaine itself. This is especially important because there may be additive or synergistic effects between cocaine and alcohol (e.g., the production of the toxin cocaethylene) or between cocaine and cigarettes (e.g., inhibition of amino acid transport across the placenta).

Most of the adopted children exposed in utero to cocaine were perceived by their parents to do well. This may reflect the tremendous plasticity of the developing brain and its ability to recover in an optimal environment, even from serious intrauterine insults.[38] These findings are encouraging and may serve to indicate that focusing resources on high-risk infants exposed in utero to cocaine may be crucial to allow them to realize their full developmental potential.

Although impossible to prove directly with the present design, our results support the view that coupling intrauterine exposure to cocaine with environmental risk factors may act as a double-edged sword for thousands of children in North America, with a tremendous long-term personal and societal burden.

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