

Effect of Benzo[a]pyrene-DNA Adduct in Cord Blood on the Neurodevelopment of 12-Month-Old Infants in Qingdao City

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Introduction: The study was designed to explore the possible adverse effects of prenatal polycyclic aromatic hydrocarbons (PAHs) on the neurodevelopment of the infants at the age of 12 months in a birth cohort in Qingdao of China. Benzo[a]pyrene (BaP)-DNA adduct level in umbilical cord blood was measured by enzyme immunoassay.

Methods: Child neurodevelopment was assessed at both 6 months and 12 months of age using the Gesell Development Inventory (GDI).

Results: This study results reveal that multivariate linear analysis, cord BaP-DNA adduct level was inversely associated with developmental quotient score in the adaptive domain [$\beta = -0.08$; 95% CI: $(-0.16, -0.003)$; $p = 0.04$], gross motor domain [$\beta = -0.10$; 95% CI: $(-0.20, -0.01)$; $p = 0.02$], fine motor domain [$\beta = -0.15$; 95% CI: $(-0.25, -0.05)$; $p = 0.01$], language domain [$\beta = -0.12$; 95% CI: $(-0.21, -0.03)$; $p = 0.02$], and personal-social domain [$\beta = -0.13$; 95% CI: $(-0.22, -0.04)$; $p < 0.01$]. Further, multivariate logistic regression analysis showed increased cord BaP-DNA adduct levels associated with increased odds of delayed in language domain.

Conclusion: In conclusion, the study suggested that prenatal PAH exposure monitored by umbilical cord blood BaP-DNA adducts may adversely affect the neurodevelopment of the infants at 12 months of age.

Keywords: neurodevelopment, PAH-DNA adducts, infant, polycyclic aromatic hydrocarbons, China

Introduction

Our previously reported cross-sectional studies have found that prenatal polycyclic aromatic hydrocarbons (PAHs) widely exist in the urban residential house dust with a high order of magnitudes in house dust and that significant association with the behavior and neurodevelopment of preschool-aged children.¹ Guo et al compared the concentrations of 12 hydroxylated polycyclic aromatic hydrocarbons in 306 urine samples collected from seven Asian countries (China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam) and found that the concentrations of 1-hydroxypyrene in Chinese participants' urine samples were 4 to 6 times higher than the other country participants.² Another biomarker of PAH exposure levels, 2-hydroxyfluorene, was also reported higher in Chinese participants than other reported countries.^{2,3} All these reported data indicated that people in China are exposed to great concentrations of PAHs as compared to other countries.

PAH exposure levels measured by airborne PAHs or biomarkers such as PAH-DNA adducts have been reported associated with the child's neurodevelopment. In

a cohort study in the USA, higher prenatal exposure to airborne PAHs was associated with decreased scores on the mental developmental index of the Bayley Scales of Infant Development-Revised at age 36 months.⁴ Further, they measured the bulky hydrophobic DNA adducts by the ³²P-postlabelling assay in umbilical cord blood and found the symptoms associated with anxiety/depression and attention problems at the age of 5 and 7 years.⁵ In an earlier China cohort near a coal-fired power, higher benzo[a]pyrene (BaP)-DNA adducts were determined by the high-performance liquid chromatography (HPLC) in umbilical cord blood and it was found with decreased scores on the Gesell test at age of 24 months.^{6,7} The period of rapid brain growth spans from the 3rd trimester of pregnancy to at least 2 years after birth.⁸ Some of the studies have been reported the prenatal PAH exposure influence on the neurodevelopment of the children less than 2 years old. Therefore, in the present analysis, we evaluated the effects of BaP-DNA adduct in umbilical cord blood, a biomarker of prenatal exposure of PAHs,^{9–12} on the neurodevelopment of children at the age of 12 months. Instead of HPLC and ³²P-post-labeled global PAH-DNA adduct detection, a quick and convenient enzyme immunoassay method was used for the measurement of PAH-DNA adduct.

Materials and Methods

Ethical Statement

This study was approved by the Ethics Committee and Institutional Review Board of Qingdao Centers for Disease Control and Prevention. The authors declare that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Study Subjects

We performed a birth cohort study in Qingdao city of China in 2014 to find the possible adverse neurodevelopmental effects of prenatal and postnatal semi-volatile organic compound exposure on the children. The pregnant women at the obstetrics of the hospitals in Qingdao city were invited to sign the informed consent for participation in this prospective cohort study. The eligible women were free from diabetes, known HIV, and known neuropsychiatric disease; they will reside in the area for at least 3 years together with their infants. The eligible children were free from birth

problems, such as delivery injuries or low birth weight; neonatal problems, such as asphyxia; intracranial hemorrhage, hypoxic-ischemic encephalopathy, and severe jaundice; acquired disabilities, including encephalitis, meningitis, encephalopathy, cerebral trauma, and cerebral injuries following convulsions; and developmental dysplasia or other developmental defects influenced by inherited metabolic diseases. In this study, the 12-month-old 348 subjects were recruited who had valid BaP-DNA adduct levels in the cord blood, of which 211 had Gesell test scores for both 6 and 12 months of age.

BaP-DNA Adduct Measurement

The umbilical cord blood was collected at the time of delivery. BaP-DNA adducts (ng/mL) were determined in extracted white blood cell DNA by OxiSelect™ BPDE DNA Adduct ELISA Kits (Cell Biolabs, Inc., San Diego, CA) according to the manufacturer's product manual.

Measures of Child Neurodevelopment

The Gesell Development Inventory (GDI) was selected in the present study for the measurement of child neurodevelopment. The GDI, was adopted by the Chinese Pediatric Association, has been validated against a Chinese reference population and widely used for assessing the child development in China.¹³ There was a significant correlation between developmental assessment at 6 to 12 months on the GDI and mental development at 6 to 7 years on the Chinese version of the Wechsler Intelligence Scales for Children.¹⁴ The GDI has been translated and standardized by the Beijing Children's Health Care Institute and consists of five behavioral domains: adaptive, gross motor, fine motor, language, and personal-social behaviors.¹⁵ Each child was assigned a developmental quotient (DQ) in each of the five specific domains. The standardized mean (\pm SD) of the DQ is 100 ± 15 , and a score < 85 indicates a developmental delay.^{16,17} All subjects were tested by a professional doctor at the Department of Child Health Care of Huangdao Maternity and Child Care Hospital of Qingdao.

Statistical Analysis

According to the product manual, the BaP-DNA adducts levels ≤ 0 ng/mL was regarded as no detection and 0 was assigned. The Shapiro-Wilk test showed that the BaP-DNA adducts were not a normal distribution, while the GDI scores could be regarded as normal distribution. Spearman's rho correlation coefficients were calculated for the BaP-DNA and the scores at age of both 6 and 12

months. The main effects of BaP-DNA adduct levels on the DQs at the age of 12 months were analyzed by multiple linear regressions with adjusted for sex, birth weight, gestational age, and maternal education. Binary logistic regression was also adopted to find the possible risk of high BaP-DNA adduct levels >90th percentile (1.945 ng/mL) on child development. DQs at age of 6 months were entered the multivariate regression model together with BaP-DNA adduct levels because of the correlation between DQs at 6 and 12 months of age. All the analyses were done with IBM SPSS Statistics version 21 (IBM Corp).

Results

The demographic characteristics, cord BaP-DNA adducts levels, and the DQ scores are shown in Table 1. The detection rate for the cord BaP-DNA adduct (> 0 ng/mL) was only 52.3% (182/348) and the median level was 0.68 ng/mL. The average scores for all DQ domains of both 6 and 12 months old were all over 90. The scores of each DQ domain were significantly correlated between 6 and 12

months of age except fine motor domain. For the language and personal-social domains, the scores indicated a significant correlation with those of all other domains (Table 2). Adduct levels showed inverse correlation with the DQ scores at the age of 12 months, but no such correlation was found for the DQ scores at the age of 6 months (data not shown).

The results of the multiple linear regression analysis are shown in Table 3. Increased cord BaP-DNA adduct level was inversely associated with DQ score decreased in the adaptive domain [$\beta = -0.08$; 95% CI: (-0.16, -0.003); $p = 0.04$], gross motor domain [$\beta = -0.10$; 95% CI: (-0.20, -0.01); $p = 0.02$], fine motor domain [$\beta = -0.15$; 95% CI: (-0.25, -0.05); $p = 0.01$], language domain [$\beta = -0.12$; 95% CI: (-0.21, -0.03); $p = 0.02$], and personal-social domain [$\beta = -0.13$; 95% CI: (-0.22, -0.04); $p < 0.01$], after adjusted for the same domain score at the age of 6 months, sex, gestational age, birth weight, and maternal education.

The frequency of developmental delay in adaptive, gross motor, fine motor, language, and the personal-social domain at the age of 12 months was 4.8%, 4.8%, 6.1%, 3.8%, and 8.2%, respectively (data not shown). Multivariate logistic regression analysis showed that increased cord BaP-DNA adduct levels associated with increased odds of delayed in language domain with OR = 5.99 (95% CI: 1.88–19.02, $p < 0.01$) (Table 4). For all domains, DQ scores at 6-month old showed positive association with 12-month-old DQs with $P < 0.05$.

Discussion

In this study, we found that the BaP-DNA adduct level in the newborn umbilical cord blood was associated with the reductions of the DQ scores at the age of 12 months. After adjusted for the DQ scores at 6 months and some other covariates, increased BaP-DNA adduct levels were significantly associated with reduced DQs at 12 months in all five domains. Our findings are consistent with the laboratory and field observations. Laboratory studies exposing experimental animals to PAHs during the prenatal period have reported impairments of memory and learning,^{18,19} as well as anxiety and depression behavior effects.^{20–22} Epidemiological studies in the USA,^{4,5,23} China,^{7,24} and Poland²⁵ had indicated neurodevelopment effects of PAHs in humans. It has been well accepted with evidence that prenatal exposure to PAHs may have an adverse effect on the neurodevelopment of children aged 2 to 8 years. Perera et al estimated the effects of prenatal exposure to airborne PAHs on neurodevelopment in children of 12 months through 36 months among inner-

Table 1 Demographic Characteristics of the Study Sample (n = 348)

Demographic Characteristic	Mean±SD (Range)
Maternal age (years)	29.0±4.1 ^{21, 45}
Maternal education (%)	
< High school	26.6
≥ High school	73.4
Sex of newborn (%female)	44.8
Birth weight (g)	3490.05±654.11 (2500, 7800)
Gestational age (week)	39.53±1.18 (35, 46)
Cord adducts (ng/mL)	1.9±3.5 (0.04, 20.08)
Detect rate (%)	182(52.3)
Median	0.68
DQs at 6 months old ^a	
Adaptive	97.3±4.8 (66, 115)
Gross motor	97.3±4.8 (77, 110)
Fine motor	98.3±6.5 (82, 114)
Language	99.8±4.8 (75, 112)
Personal-social	98.3±6.2 (80, 118)
DQs at 12 months old ^a	
Adaptive	98.7±6.5 (81, 119)
Gross motor	101.6±8.7 (80, 156)
Fine motor	103.0±9.0 (74, 154)
Language	96.4±6.9 (72, 136)
Personal-social	102.7±8.0 (84, 133)

Note: ^an = 211.

Abbreviations: DQ, developmental quotient; SD, standard deviation.

Table 2 Spearman's Rho Correlation Coefficients Between Adduct Levels and DQs at 6 Months and 12 Months Old

DQs at 6 Months Old	DQs at 12 Months Old				
	Adaptive	Gross Motor	Fine Motor	Language	Personal-Social
Adaptive	0.158*	0.186**	0.099	0.148*	0.096
Gross motor	0.171*	0.277**	0.093	0.170*	0.240**
Fine motor	0.071	0.089	0.131	0.115	0.137*
Language	0.302**	0.279**	0.232**	0.232**	0.220**
Personal-social	0.163*	0.264**	0.195**	0.170*	0.234**

Notes: ** $p < 0.01$; * $p < 0.05$.

Table 3 Results of Multiple Linear Regression Analyses of DQ Scores at 12 Months of Age and Cord BaP-DNA Adducts ($n = 211$)^a

DQ Score	Variable	β (95% CI)	p
Adaptive	BaP-DNA adduct Adaptive-6mon	-0.08(-0.16, 0.003) 0.14(0.04, 0.23)	0.04 0.01
Gross motor	BaP-DNA adduct Gross motor-6mon	-0.1(-0.20, -0.01) 0.31(0.20, 0.41)	0.02 <0.01
Fine motor	BaP-DNA adduct Fine motor-6mon	-0.15(-0.25, -0.05) 0.1(-0.01, 0.21)	0.01 0.07
Language	BaP-DNA adduct Language-6mon	-0.12(-0.21, -0.03) 0.18(0.09, 0.28)	0.02 <0.01
Personal-social	BaP-DNA adduct Personal-6mon	-0.13(-0.22, -0.04) 0.21(0.11, 0.31)	<0.01 <0.01

Note: ^aModel includes sex, gestational age, birth weight, and maternal education.

Abbreviation: CI, confidence interval.

city children by a general estimated equation. At 36 months, the adverse effects on a child's cognitive development were significantly greater for high-exposed ($>4.16 \text{ ng/m}^3$)

compared to low-exposed ($\leq 4.16 \text{ ng/m}^3$) children.⁴ Edwards et al found in a cohort of pregnant, healthy, non-smoking women in Poland that higher (above the median of 17.96 ng/m^3) prenatal exposure to airborne PAHs associated with decreased Raven Colored Progressive Matrices Scores at the age of 5 years.²⁵ As the biomarker of airborne PAHs exposure, cord blood BaP-DNA adduct measured by HPLC showed positive association with symptoms of anxious/depressed and attention problems at the age of 6 to 7 years.²³ In another earlier study in china, cord blood BaP-DNA measured by HPLC indicated an association with the delayed development in the motor and language domain of the children aged 2 years.⁷ To the best of our knowledge, the association between prenatal PAH exposure and the child's neurodevelopment at 12 months had not been detected. Perera et al investigated the effects of prenatal airborne PAH exposure on the child's neurodevelopment at 12, 24, and 36 months. However, no effects of PAH on cognitive development at 12 and 24 months were found.⁴ Thus, we are the first to report the possibly significant effect on a child's development at the age of 12 months.

Table 4 Results of Multivariate Logistic Regression Analyses of DQ Scores at 12 Months of Age and Cord BaP-DNA Adducts ($n = 211$)^a

DQ Score	Variable	β	OR (95% CI)	p
Adaptive	BaP-DNA adduct Adaptive-6mon	0.98 -0.37	2.66 (0.17, 41.45) 0.69 (0.56, 0.86)	0.49 <0.01
Gross motor	BaP-DNA adduct Gross motor-6mon	0.13 -0.18	1.14 (0.22, 5.89) 0.84 (0.75, 0.94)	0.88 <0.01
Fine motor	BaP-DNA adduct Fine motor-6mon	2.07 -0.56	7.95 (0.30, 211.57) 0.57 (0.39, 0.85)	0.22 <0.001
Language	BaP-DNA adduct Language-6mon	1.79 -0.09	5.99 (1.88, 19.02) 0.91 (0.83, 1.00)	<0.01 0.05
Personal-social	BaP-DNA adduct Personal-6mon	0.19 -0.26	1.21 (0.09, 15.90) 0.77 (0.64, 0.92)	0.89 <0.01

Note: ^aModel includes sex, gestational age, birth weight, and maternal education.

Abbreviations: OR, odds ratio; CI, confidence interval.

We adopted the enzyme immunoassay in this study for the rapid detection of BaP-DNA adducts. This is the first time to use this method to detect BaP-DNA adducts as the PAH exposure measure to investigate the possible PAH effect on the neurodevelopment, although this method has been successfully used recently in some studies like for cell,^{26,27} swine,²⁸ or human.²⁹ It seemed that the adverse effects found in 12 months of age in our study were earlier than those reported in other studies. However, it is difficult to compare our BaP-DNA adduct levels with other studies by HPLC or ³²P-post-labeled global PAH-DNA adduct. The unit ng/mL is used in the enzyme immunoassay, while adduct count/10⁸ nucleotides are used in HPLC and ³²P-post-labeled analysis. It was inappropriate to convert from one unit to another, especially for ³²P-post-labeled global PAH-DNA adduct which formed by a range of hydrophobic aromatic hydrocarbons in addition to PAH, such as nitro-aromatic compounds³⁰ and heterocyclic amines.³¹ A strong reason for our enzyme immunoassay using is the convenience of its commercial ELISA kit compared to the HPLC complication and the safety compared to the possible radioactivity of ³²P-post-labeled analysis. The BaP-DNA standard in the kit was created in vitro by incubating calf thymus DNA with BPDE-I (NCI Carcinogen Repository MRI 477). The producer pointed out that it is difficult to identify how many BPDE modifications per DNA molecule. Therefore, the OD values cannot be converted to pmol/μg DNA. Thus, the unit ng/mL was used in the present study. However, the detection rates are still comparable between studies although the units are different. The current study suggested a lower detection rate of BaP-DNA adduct compared with another Chinese report for the Tongliang children living near to a coal-fired power plant (52% vs 80%).⁷ But our detection rate is comparable to that of a cohort without special exposure in the USA (45~50%).^{32,33}

The main limitation of the present study was that we lacked air PAH monitoring data for all three trimesters. The umbilical cord blood PAH-DNA adduct from the prenatal PAH exposure is influenced by the mother's metabolic and detoxifying enzymes and dietary habit. Therefore, we were not able to identify the predominant exposure of these three periods. We also did not measure postnatal personal air PAH exposure and were unable to adjust directly for postnatal PAH exposure. We also lacked other known prenatal and postnatal neurotoxicant exposure from breast milk, infant complementary foods, or other ambient environment media. Future studies should

continue to examine the influence of the postnatal PAH and other possible neurotoxicant exposure and to confirm the present findings.

In this study, we showed that prenatal PAH exposure monitored by umbilical cord blood BaP-DNA adduct at levels recently encountered in the infants at the age of 12 months of Qingdao City may adversely affect the neurodevelopment of the infants. Our findings should be carefully interpreted and require further confirmation but of potential concern because of the quick and convenient performance at the clinics with an ELISA kit for the BaP-DNA adduct measure and the widely used Gesell Development Inventory for the neurodevelopment assessment in China. We are continuing to follow this cohort to determine the long-term effects of prenatal PAH exposure and the possible confounding influences of the postnatal PAH exposure on the neurodevelopment of the children.

Author Contributions

Yong Zhang, Yuehua Yang, and Qian Zhang are considered first authors. Zulqarnain Baloch and Bingling Wang designed the research and supervised the whole process; Yong Zhang, Yuehua Yang, Qian Zhang, and Jing Cui finished the lab work, as well as statistical analysis, and were responsible for manuscript writing and revising. Abdul Rahaman, Xiao-Rong Huang, YaSu, and Ruqin Gao were responsible for data and sample collection and take part in lab work. All authors contributed to data analysis, drafting, and revising the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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