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Neurodevelopment of Infants with Prenatal Exposure to Polybrominated Diphenyl Ethers

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Abstract The study aimed to examine the impact of prenatal exposure to polybrominated diphenyl ethers (PBDEs) on infant neurodevelopment. PBDEs levels in 36 cord blood samples were analyzed with a high-resolution-gas-chromatograph/high-resolution-mass-spectrometer and infant neurodevelopment was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition. The mean and median of Σ_{11}PBDEs were 6.63 and 4.63 ng/g lipid, respectively. As compared to the lower PBDEs group (Σ_{11}PBDEs < 4.63 ng/g lipid), the higher PBDEs group (Σ_{11}PBDEs > 4.63 ng/g lipid) had a significantly higher actual odds ratio (OR $= 1.13$, $p < 0.05$) of the cognition score as well as a lower odds ratio (OR $= 0.904$, $p < 0.01$) of the adaptive behavior score, suggesting that prenatal PBDEs exposure may potentially affect infant neurodevelopment.

Keywords Polybrominated diphenyl ethers (PBDEs) · Cord blood · Infants · Neurodevelopment · Bayley scale of infants and toddlers development

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Polybrominated diphenyl ethers (PBDEs), a class of brominated flame retardants, are widely used in various commercial products, such as furniture, textiles, paints, construction materials, and household electronic equipment (de Wit 2002). Human exposure to PBDEs has been a growing global concern due to its bioaccumulation and toxicity (Darnerud et al. 2001). Results from animal studies have suggested that PBDEs are neurotoxicants (Costa and Giordano 2007). However, evidence showing adverse impacts of prenatal PBDEs exposure on human neurodevelopment or health remains limited (Birnbaum and Cohen Hubal 2006). PBDE levels in infants and children are higher than those in adults (Toms et al. 2009). Analysis of paired samples revealed significantly higher PBDEs levels in cord blood than in breast milk (Gómara et al. 2007). Prenatal or postnatal exposure of mice or rats to PBDEs has been shown to cause persistent neurobehavioral defects, i.e., changes in locomotor activity, cognitive effects, spontaneous behavior, and cholinergic susceptibility (Costa and Giordano 2007). Only two reports have found a correlation between prenatal PBDE exposure and developmental neurotoxicity in infants or young children (Roze et al. 2009; Herbstman et al. 2010). In our recent studies

(Chao et al. 2007, 2010a, 2010b; Wang et al. 2008; Koh et al. 2010), increased PBDE levels in breast milk were statistically linked to older age of mothers and to lower BMI during pregnancy, lower education level, occupational exposure, a prolonged menstruation period, and irregular menstrual cycle of mothers as well as lower birth outcomes of their offspring.

Materials and Methods

Healthy mother-infant paired participants were randomly recruited from four local hospitals in southern Taiwan between April 2007 and December 2008. The pregnant participants were interviewed by our researchers at the obstetrics clinics during routine health check-ups. The participants' offspring were brought to pediatric outpatient clinics. The study protocol was reviewed and approved in 2007 by the Human Ethical Committee of Pingtung Christian Hospital, Taiwan and the study was performed according to the ethical standards of the Helsinki Declaration of 2004. Prior to enrollment, all participants gave their informed consent after receiving detailed explanations of the study and potential consequences. More than 160 pregnant women were invited to join this program; 95 of them agreed to answer a detailed questionnaire used to elicit information regarding age, pre-pregnancy BMI, parity, socioeconomic status, smoking and dietary habits, and possible PBDEs exposure from electronics. Eighty mothers who voluntarily donated cord blood were enrolled initially. Among the 80 cord blood samples collected, the insufficient volume of 26 samples was excluded and the rest of 54 sufficient samples were eligible for further chemical analysis. When they reached 8–12 months of age, 36 of the 54 infants returned to the hospital for assessment by the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).

PBDE standards and ^{13}C-labeled PBDE standards were purchased from Cambridge Isotope Laboratories (Andover, MA, USA) and Wellington Laboratories (Guelph, Canada), respectively. The highest-quality sodium sulfate, alumina oxide, potassium oxalate, and silica gel were obtained from Merck (Darmstadt, Germany). Methods for analyzing cord-blood PBDEs have been previously described (Lin et al. 2011). Following delivery, each umbilical cord blood sample was collected into two 6-mL tubes and a 120-mL glass bottle. Cord blood samples were immediately separated by centrifugation and the cord serum was stored at −80°C. Cord-serum samples (20–25 mL of each) were sent to chemical analysis (Supermicro Mass Research and Technology Center, Cheng Shiu University, Taiwan). Briefly, PDBEs were extracted from cord serum, the extract was cleaned up by passing three multicolumns, and PDBEs in the eluate were concentrated by a stream of nitrogen gas. The eluates were analyzed for 11 PBDE congeners (BDE-15, 28, 47, 49, 99, 100, 153, 154, 183, 196, and 197) using a high resolution gas chromatograph (Hewlett-Packard 6970) and a high resolution mass spectrometer (Micromass Autospec Ultima) coupled with a DB-5HT column (L = 15 m, i.d. = 0.25 mm, film thickness = 0.1 μm) (J&W Scientific, Folsom, CA, USA) in splitless mode.

The neurodevelopment of infants (age, 8–12 months) was examined by psychologists who used the Bayley-III (Bayley 2006), to evaluate cognitive, language (receptive and expressive communication), and motor (fine and gross) ability. Parent-report questionnaires were incorporated to assess social-emotional and adaptive behavior. The assessment provides a developmental quotient, which takes into account raw scores and chronological age (adjusting for prematurity), and generates continuous scores on five scales (cognitive, language, motor, social-emotional, and adaptive behavior). A standard score for the Bayley-III with a mean of 100 and a standard deviation (SD) of 15 was derived for each scale. Statistical analyses of Spearman's rho correlation coefficient and binary logistic regression tests with 2,000 bootstrap samples were carried out using SPSS version 19 (IBM SPSS Statistics 19).

Results and Discussion

Descriptive statistics of variables in the study are shown in Table 1. The means and medians of maternal age, pre-pregnancy BMI, and parity were 29.8 and 28.5 years old, 22.6 and 21.2 kg/m^2, and 1.94 and 2.00 persons, respectively. The number of women with 1, 2, 3, and 4 parity was 12, 16, 6, and 2, respectively. Subscores on the Bayley-III were 105 ± 11.6 (cognitive), 99.4 ± 10.0 (language), 99.6 ± 8.40 (motor), 98.6 ± 17.0 (social-emotional), and 98.3 ± 14.3 (adaptive behavior). Table 2 shows the 11 PBDE congener levels in the 36 cord blood samples. The mean and median of Σ_{11}PBDEs, and the sum of BDE-15, 28, 47, 49, 99, 100, 153, 154, 183, 196, and 197 in the cord blood samples were 6.63 and 4.63 ng/g lipid, respectively.

Table 3 shows that maternal age is significantly correlated with increased levels of BDE-28, 47, 100, 153, and 154 in cord blood, but not with Σ_{11}PBDEs. Our result is consistent with the findings of the Herbstman's report (Herbstman et al. 2007). However, a non-significant correlation between maternal age and cord serum levels of BDE-28, 47, 100, 153, and 154 was shown elsewhere (Kang et al. 2010). No significant association was found between cord blood PBDEs and pre-pregnancy BMI, parity, education level, or annual household income in our present study. Most previous studies revealed non-significant association between BMI and levels of PBDEs in cord blood (Vizcaino

Table 1 Descriptive statistics of the study's participants (n = 36)

	Mean	Median	SD	Range
Mothers				
Age (years)	29.8	28.5	4.88	23.0–41.0
Pre-pregnancy BMI (kg/m^2)	22.6	21.2	4.52	17.2–34.9
Parity (number)[a]	1.94	2.00	0.860	1.00–4.00
Infants				
Gestational age (weeks)	38.5	38.0	1.29	36.0–40.0
Weight (g)	3,350	3,350	433	2,450–4,120
Length (cm)	49.8	50.0	1.97	47.0–55.0
Head circumference (cm)	34.1	34.0	1.33	32.0–36.0
Chest circumference (cm)	33.0	33.0	1.71	28.5–36.0
Neurodevelopment Score of newborns				
Apgar score at 1 min (score)	7.90	8.00	0.575	6.00–9.00
Apgar score at 5 min (score)	8.99	9.00	0.211	7.00–10.0
Bayley-III scores of infant development				
Cognitive scale (score)	105	105	11.6	85.0–130
Language scale (score)	99.4	100	10.0	77.0–118
Motor scale (score)	99.6	100	8.40	82.0–115
Social-emotional scale (score)	98.6	100	17.0	65.0–130
Adaptive behavior scale (score)	98.3	102	14.3	69.0–131

[a] The number of women with parity 1, 2, 3, and 4 was 12, 16, 6, and 2, respectively

Table 2 PBDE levels in cord blood of 36 Taiwanese mothers (ng/g lipid)

PBDEs	N > LODs[a]	Mean	Median	SD	Range
BDE-15	33 (91.7%)	0.155	0.130	0.118	<LOD[b]–0.678
BDE-28	20 (55.5%)	0.180	0.116	0.155	<LOD–0.598
BDE-47	36 (100%)	1.40	0.702	3.16	0.351–19.6
BDE-49	34 (94.4%)	0.136	0.094	0.114	<LOD–0.576
BDE-99	36 (100%)	0.726	0.689	0.641	0.194–3.93
BDE-100	33 (91.6%)	0.466	0.163	1.69	<LOD–10.3
BDE-153	36 (100%)	1.39	0.915	2.41	0.292–14.7
BDE-154	35 (97.2%)	0.140	0.113	0.103	<LOD–0.546
BDE-183	22 (61.1%)	0.709	0.505	1.26	<LOD–9.30
BDE-196	24 (66.7%)	0.262	0.186	0.183	<LOD–0.803
BDE-197	36 (100%)	1.01	0.652	0.958	0.261–5.10
Σ_{11}PBDEs	345 (87.1%)	6.63	4.63	8.17	2.24–49.1

[a] N: sample number; >LODs: higher than limits of detection

[b] <LOD: lower than limits of detection

et al. 2010) as well as in breast milk (Herbstman et al. 2007; Thomsen et al. 2010). However, our previous report (Wang et al. 2008) and a large-scale study (n = 1367) by Lim et al. (2008) demonstrated a negative correlation between levels of PBDEs and BMI. A Spanish study (Vizcaino et al. 2010) and our present studies revealed no significant association between maternal education level and cord blood levels of PBDEs. Still, other studies found positive (Herbstman et al. 2007) and negative (Thomsen et al. 2010) correlation between breast milk PBDEs and education level. On the basis of these results, there is currently no agreement on whether PBDE exposure is associated with maternal age, BMI, or education level. Large-scale epidemiological studies are encouraged.

Table 4 shows the results of the assessment of infant neurodevelopment using the Bayley III. Odds ratio (OR) of low cognitive score was significantly higher in groups with higher BDE-15, 99, 197, or Σ_{11}PBDEs than in those with

Table 3 Correlations between levels of cord-blood PBDEs and maternal characteristics

PBDEs	Maternal age	Pre-pregnancy BMI	Parity[a]	Education level[b]	Annual income[c]
BDE-15	0.178[d]	−0.019	0.216	−0.125	0.141
BDE-28	0.330*	0.060	−0.031	−0.073	0.172
BDE-47	0.350*	0.142	−0.051	−0.015	0.214
BDE-49	0.239	0.070	0.127	−0.140	0.128
BDE-99	0.071	0.043	0.213	0.094	0.095
BDE-100	0.334*	0.157	−0.096	−0.190	−0.005
BDE-153	0.376*	−0.147	0.007	−0.036	0.198
BDE-154	0.368*	−0.106	−0.035	−0.127	0.217
BDE-183	0.050	−0.130	0.010	−0.230	0.034
BDE-196	0.215	−0.257	0.120	−0.097	0.123
BDE-197	0.169	−0.171	−0.106	−0.090	0.016
Σ_{11}PBDEs	0.320	−0.028	−0.016	−0.073	0.177

[a] Parity: 0 (uniparas), 1 (biparas), 2 (triparas), 3 (quadriparas)

[b] Ordinal levels of education: 0 (<high school), 1 (high school), 2 (junior college), 3 (university or higher)

[c] Ordinal levels of annual house income: 0 (<$10,000 US dollars), 1 ($10,000–$19,999), 2 ($20,000–$33,399), 3 ($33,400–$50,000), 4 (>$50,000)

[d] Spearman's rho correlation coefficient based on 2,000 bootstrap samples

* $p < 0.05$

lower BDE-15, 99, 197, or Σ_{11}PBDEs. Adaptive behavior scores were negatively related to cord blood levels of BDE-28, 99, 154, 183, and Σ_{11}PBDEs. Scores on the language, motor, and social-emotional scales were not linked to levels of Σ_{11}PBDEs and certain PBDEs. A previous study on neurodevelopment in infants or toddlers assessed by Bayley Scales for Infant Development, second edition, (BSID-II) demonstrated that the cord-blood BDE-47 level was inversely correlated with the 12-month Psychomotor Development Index (PDI), the 24-month Mental Development Index (MDI), and the 48-month full-scale and verbal IQ (Herbstman et al. 2010). Meanwhile, the BDE-99 level was correlated with the 24-month MDI as well as the 48-month full-scale and verbal IQ, and the BDE-100 level was associated with the 24-month MDI, the 36-month MDI, the 48-month full-scale and verbal IQ, and the 48-month and 72-month performance IQ. Using the Wechsler Preschool and Primary Scale of Intelligence, Revised Edition (WPPSI-R) to evaluate the neurodevelopment of 5–6-year-old children with in utero exposure to PBDEs (measured in maternal serum on the 27th gestational week), Roze et al. indicated negative associations between sustained attention and levels of BDE-47, -99, and -100, between verbal memory and level of BDE-153, and between fine manipulative abilities and level of BDE-154, and positive correlations for total behavioral outcome and levels of BDE-99 and -100 and for internalizing behavior and levels of BDE-47, -99, and -100 (Roze et al. 2009). Using the McCarthy scales of Children's Abilities, a recent study assessed the motor and cognitive function of 4-year-old children with prenatal and postnatal PBDE exposures and found no correlation with prenatal and postnatal exposure to BDE-47, -99, and -100 and Σ_3PBDEs (Gascon et al. 2011).

Our present study in infants at 8–12 months showed that Σ_{11}PBDEs had a positive correlation with cognition, but a negative correlation with adaptive behavior. Several factors that could influence infant neurodevelopment, including intelligence quotient and education level of mothers, socioeconomic position, and smoking during pregnancy, were not considered. Although most studies in rodents agree with findings in humans that prenatal or neonatal PBDE exposure delays neurodevelopment, some in vivo studies report different findings (Costa and Giordano 2007). Several factors may account for differences between our present results and those of some recent studies (Roze et al. 2009; Herbstman et al. 2010; and Gascon et al. 2011), including the evaluation tool used (Bayley-III vs. BSID-II, WPPSI-R, and McCarthy scales of Children's Abilities), levels of exposure to PBDE congeners (i.e., teraBDEs to heptaBDEs, and BDE-196 and 197 in addition), sample size (36 in our study vs. 98–118 in Herbstman et al., 62 in Roze et al., and 88–244 in Gascon et al.), exposure pattern (the predominant role of BDE-153 in our study and Roze et al. vs. BDE-47 in Herbstman et al. and Gascon et al.), and the age of study participants (8–12 months old in our study vs. 1–4 years old in Herbstman et al., 5–6 years old in Roze et al., and 4 years old in Gascon et al.). Based on the limited findings of current reports, exposure to PBDEs in uterus or during the early stage of life in humans

Table 4 Odds ratios of the neurodevelopment as indicated by Bayley-III scores in higher PBDE exposure groups (n = 18) and lower PBDE exposure groups (n = 18)[a]

PBDEs	Groups (ng/g lipid)	Bayley-III scale scores				
		Cognitive	Language	Motor	Social-emotional	Adaptive behavior
BDE-15	<0.130[b]	1.00	1.00	1.00	1.00	1.00
	>0.130	1.17**	1.04	1.06	0.997	0.953
BDE-28	<0.116[b]	1.00	1.00	1.00	1.00	1.00
	>0.116	1.02	1.01	0.978	0.979	0.915*
BDE-47	<0.702[b]	1.00	1.00	1.00	1.00	1.00
	>0.702	1.04	1.03	0.989	0.977	0.942
BDE-49	<0.094[b]	1.00	1.00	1.00	1.00	1.00
	>0.094	0.985	0.969	0.970	0.986	0.936
BDE-99	<0.689[b]	1.00	1.00	1.00	1.00	1.00
	>0.689	1.10*	1.02	0.985	0.966	0.934*
BDE-100	<0.163[b]	1.00	1.00	1.00	1.00	1.00
	>0.163	1.01	1.01	1.03	0.991	0.991
BDE-153	<0.915[b]	1.00	1.00	1.00	1.00	1.00
	>0.915	0.978	0.943	1.02	0.972	0.976
BDE-154	<0.113[b]	1.00	1.00	1.00	1.00	1.00
	>0.113	1.03	1.02	1.03	0.979	0.824**
BDE-183	<0.505[b]	1.00	1.00	1.00	1.00	1.00
	>0.505	1.06	0.971	0.990	0.991	0.931*
BDE-196	<0.186[b]	1.00	1.00	1.00	1.00	1.00
	>0.186	0.983	0.973	1.03	1.02	0.962
BDE-197	<0.652[b]	1.00	1.00	1.00	1.00	1.00
	>0.652	1.19*	1.15	1.06	0.995	0.946
Σ_{11}PBDEs	<4.63[b]	1.00	1.00	1.00	1.00	1.00
	>4.63	1.13*	1.03	1.06	0.966	0.904**

[a] Odds ratios based on 2000 bootstrap samples after adjustment for maternal age, pre-pregnancy BMI, and parity

[b] Reference control

* $p < 0.05$

** $p < 0.01$

probably have potential impact on the neurodevelopment of infants or children.

In conclusion, prenatal exposure to PBDEs was found to affect the cognitive skill and adaptive behavior of infants in the present study. Furthermore, our finding that high cord-blood levels of Σ_{11} PBDEs and certain PBDEs (e.g., BDE-99) delay adaptive behavior development in infants was consistent with findings of neurotoxicity by most in vivo studies. Although only 36 infants were examined in this study, we used a bootstrap method (n = 2,000) to decrease the statistical and sampling bias resulting from small samples. Large-scale and longitudinal studies to examine association between PBDEs exposure and the neurodevelopment of neonates or children are needed.

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