PERINATAL DIOXIN EXPOSURE AND NEURODEVELOPMENT OF CHILDREN AGED 3 YEARS – A FOLLOW UP STUDY IN VIETNAM

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Introduction

Adverse effects of polychlorinated biphenyls (PCBs) and dioxins on neurodevelopment of children at early life were reported in some populations worldwide[1,2]. These studies suggested that dioxins may exert adverse effects on infant neurodevelopment, even in populations with background levels of exposure.

In South Vietnam, the use of the herbicides during the Vietnam War represents a major source of dioxin exposure[3]. Residents living near former US airbase- which is recently considered as a "hot spot" of dioxin contamination in Vietnam – still are suffering a high dioxin exposure[4]. As the brain at fetus and infant stage is the most vulnerable to neurotoxicants, it raised concerns about the effect of dioxin exposure on infant development in these areas. We set up a mother-infant cohort in a "hot spot" of dioxin contamination in Vietnam since 2008. The mother-infant pairs were followed up since birth and at certain periods of infant development. We had examined the infant neurodevelopment at 4 months and 1 years of age. The relationships of perinatal dioxin exposure with infant neurodevelopment at 4 months and 1 years of age were reported elsewhere[5,6]. In the present study, we extended follow-up period for 3years and investigated the effects of perinatal exposure to dioxins on neurodevelopment of children aged 3 years. #

Materials and methods

The Thanh Khe districts of Da Nang city are located about 3 km from the airbase and were thus chosen as the location for the present study. The baseline subjects for the study were 158 mother-infant pairs who were recruited when mother came to give birth in the obstetric department of Thanh Khe district hospital. The criteria for recruitment were as follows: mothers must have resided in the district for a period encompassing at least the duration of their pregnancy; mothers must have given birth to full-term babies; and there must have been no complications during childbirth. Information was collected for the mothers (age, residence history, parity, height, weight, smoking habits, alcohol consumption, employment, education, and economic status), fathers (age, education, income, smoking and drinking habits) and the infants (gestational age, gender, and breastfeeding status).

A breast milk sample was collected from each nursing mother at 1 month after birth and was used to quantify the levels of 17 different 2,3,7,8-substitued polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) congeners. Toxic equivalence for total 17 congeners (total TEQ) was calculated basing on the WHO 2005-TEF. The daily dioxin intake (DDI) of nursing infants at 1 month was estimated with the following equation:

DDI = (volume of milk per day in ml) × (% lipid content of milk/100) × (total TEQ in breast milk in pg/g of lipid)/(infant weight in kg at 1 month of age). Dioxin concentrations in breast milk and DDI of infants were considered as indexes of dioxin exposure during perinatal period of infants.

Infants were followed up when they were approximately 3 years old (37±1.8 months), and examined health and developmental condition. The Bayley Scales of Infant and Toddler Development, third edition (Bayley III), was

assessed to evaluate infant neurodevelopmental status, cognitive, language [receptive communication (RC) and expressive communication (EC)], motor [fine motor (FM) and gross motor (GM)] development.
Simple correlations between the perinatal dioxin exposure indexes and neurodevelopment scores of 3 years-old children were investigated. Subjects were divided into two groups with cutoff value being 75 %tile point of total TEQ (18.9 pg/g fat). Comparisons of neurodevelopmental scores between 2 groups at different dioxin exposure levels were performed using generalized linear model. The SPSS software package (ver. 21.0) was used for data analysis.

Results and discussion

At the 3-year- old survey, 122 mother-infant pairs were followed up (77.2%). The average characteristics of subjects are presented in Table 1. The mean age of mothers and fathers was 28.6 and 34.8 years, respectively. No mother was a smoker, but 77.9% of fathers smoked. The rate of boys was 50.8% and the rate of first child was 28.7%.
The mean levels of TCDD and total TEQ in breast milk and DDI of infants were 1.6 and 13.6 and 79.1 pg/g fat, respectively. These values were approximately 4- fold higher than those of mothers living in non-sprayed areas[4].
Table 2 showed the Spearman's rho correlation coefficients between dioxin exposure indexes and neurodevelopment scores of children aged 3 years. All dioxin congeners (except PeCDD), TEQ of PCDDs and PCDFs, total TEQ and DDI of infants showed negative correlations with all aspects of neurodevelopment. In the language domain, 11 dioxin congeners showed significant and negative correlations with receptive communication (RC). Among them, 10 congeners (except OCCD) remained significant relationships with language composite score (LCS), which was a composition of both RC and expressive communication (EC). DDI of infants also showed significant negative relationships with both RC and LCS. We had previously reported that social–emotional development of the 1-year-old infants was associated with the TEQ of furans, and expressive language was associated with specific congeners of dioxins and furans[6] .
When children were divided into two groups, the lower exposure group with total TEQ < 75 percentile and the higher exposure one with total TEQ ≥ 75 percentile, the scores of Bayley were compared between these two groups by general linear model after adjustment for covariates including mother's age, parity (primi1, multi2), education years, infant gender (boy1, girl2), family smoking, alcohol drinking during pregnancy (n0,y1), family income (VND), gestational weeks, birth weight of infant. At this time, value of 75 percentile of total TEQ was 18.9 pg/g fat. The scores of cognitive and motor domains in ≥ 75 percentile group were 3.3 and 6.5 point, respectively, which were significantly lower than those in <75 percentile group. The language score in ≥75 percentile group was lower than that in <75 percentile group (95.6 vs 92.2), but difference was not significant.
In conclusion, the perinatal dioxin exposure was adversely associated with various aspects of neurodevelopment of children aged 3 years living in a hot spot of dioxin contamination in Vietnam.

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References

1. Koopman-Esseboom C, Weisglas-Kuperus N, Ridder MAJ, Van der Paauw CG, Tuinstra LGMTh, and Sauer PJJ. 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. *Pediatrics* 97:700-706.
2.#Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N et al. 2006. Effects of Prenatal Exposure to Polychlorinated Biphenyls and Dioxins on Mental and Motor Development in Japanese Children at 6 Months of Age. *Environ Heath Perspect* 114 (5):773-778.
3. Schecter A, Quynh HT, Päpke O, Tung KC, Constable JD. 2006. Agent Orange, Dioxins, and Other Chemicals of Concern in Vietnam: Update 2006. *J Occup Environ Med.* 48(4), 408-413

4. Tai PT, Nishijo M, Kido T, Nakagawa H, Maruzeni S, Naganuma R, Anh NT, Morikawa Y, Luong HV, Anh TH, Hung NN, Son LK, Tawara K, Nishijo H. (2011) *Environ Sci Technol.* 45, 6625-6632
5. Tai PT, Nishijo M, Anh NTN, Maruzeni S, Nakagawa H, Luong HV, Anh TH, Honda R, Kido T, Nishijo H. Dioxin exposure in breast milk and infant neurodevelopment in Vietnam. *Occup Environ Med* 2013;00:1–6. doi:10.1136/oemed-2012-1010216.
6. Tai PT, Nishijo M, Nakagawa H, Maruzeni S, Anh NTN, Morikawa Y, Luong HV, Anh TH, Son LK, Nishijo H. Associations of Perinatal Dioxin Exposure with the Neurodevelopment of Vietnamese Infants. *AJE* (in press)

Table 1 Characteristics of parents and infants

		N	Mean, %	SD	Min.	Max
Children factor						
Age	months	122	37.0	1.8	33	40
Gestational weeks		121	39.5	0.8	37	41
Birth weight	g	122	3239.8	380.1	2324	4616
Rate of boys	%	122	50.8			
Rate of the first child	%	122	28.7			
Maternal factor						
Age	years	122	28.6	6.1	18	42
Education	years	118	8.3	3.5	0	14
Income	VND	119	2201.3	1514.2	0	10000
Weight	kg	119	56.9	7.1	42	71
Height	cm	119	154.2	4.9	141	176
Smoking rate	%		0.0			
Drinking habit	%		0.0			
Paternal factor						
Age	years	117	34.8	6.2	23	54
Education (years)	years	116	9.6	2.6	0	12
Income (VND)	VND	117	3399.1	2040.0	0	10000
Smoking rate	%	118	77.9			
Drinking frequency	days/week	118	2.3	2.1	0	7

VND: Vietnamese Dong

Table 2 Spearman's rho correlation coefficients between dioxin exposure indexes and neurodevelopment scores

	CCS	RC	EC	LCS	FM	GM	MCS
	r	r	r	r	r	r	r
TCDD	-0.063	-0.077	-0.133	-0.108	-0.033	-0.164	-0.111
PeCDD	0.030	-0.097	-0.059	-0.083	-0.030	-0.144	-0.089
HxCDD1	-0.006	-0.147	-0.117	-0.148	-0.046	-0.147	-0.103
HxCDD2	-0.020	-0.161	-0.114	-0.151	-0.054	-0.146	-0.110
HxCDD3	-0.079	-.222*	-0.165	-.208*	-0.049	-0.083	-0.076
HpCDD	-0.013	-.205*	-0.160	-.192*	-0.069	-0.134	-0.120
OCDD	-0.035	-.201*	-0.109	-0.155	-0.049	-0.119	-0.102
TCDF	-0.069	-0.155	-0.007	-0.096	-0.105	0.010	-0.071
PeCDF1	-0.155	-.330**	-.196*	-.307**	-.214*	-0.082	-.191*
PeCDF2	-0.068	-0.163	-0.071	-0.131	-0.118	-0.123	-0.124
HxCDF1	-0.134	-.239*	-0.096	-.189*	-0.120	-0.088	-0.116
HxCDF2	-0.130	-.238*	-0.110	-.196*	-0.145	-0.117	-0.147
HxCDF3	-0.143	-.202*	-.190*	-.215*	-0.096	0.004	-0.071
HxCDF4	-0.104	-.261**	-0.151	-.223*	-0.102	-0.138	-0.137
HpCDF1	-0.102	-.253**	-0.154	-.213*	-0.088	-0.073	-0.102
HpCDF2	-0.119	-.244*	-.219*	-.254**	-0.144	-0.021	-0.125
OCDF	-.252**	-.253**	-0.119	-.192*	-0.054	-0.075	-0.060
TEQ-PCDDs	-0.001	-0.114	-0.118	-0.119	-0.026	-0.161	-0.100
TEQ-PCDFs	-0.114	-.216*	-0.087	-0.170	-0.132	-0.112	-0.133
Total TEQ	-0.053	-0.169	-0.104	-0.146	-0.075	-0.143	-0.116
DDI	-0.173	-.229*	-0.082	-.193*	-0.158	-0.101	-0.127

** Correlation is significant at the 0.01 level.* Correlation is significant at the 0.05 level (2-tailed).

CCS: Cognitive composite score, RC: Receptive Communication, EC: Expressive Communication

LCS: Language Composite Score, FM: Fine Motor, GM: Gross Motor, MCS: Motor Composite Score

r: Spearman's rho correlation coefficient

TCDD: 2,3,7,8-TetraPCDD, PeCDD: 1,2,3,7,8-PentaCDD, HxCDD1: 1,2,3,4,7,8-HexaCDD, HxCDD2: 1,2,3,6,7,8-HexaCDD, HxCDD3: 1,2,3,7,8,9-HexaCDD, HpCDD: 1,2,3,4,6,7,8-HeptaCDD OCDD: OctaCDD, TCDF: 2,3,7,8-TetraCDF, PeCDF1: 1,2,3,7,8-PentaCDF, PeCDF2: 2,3,4,7,8-PentaCDF, HxCDF1: 1,2,3,4,7,8-HexaCDF, HxCDF2: 1,2,3,6,7,8-HexaCDF, HxCDF3: 1,2,3,6,8,9-HexaCDF, HxCDF4: 2,3,4,6,7,8-HexaCDF, HpCDF1: 1,2,3,4,6,7,8-HeptaCDF, HpCDF2: 1,2,3,4,7,8,9-HeptaCDF, OCDF: OctaCDF