THE EFFECT OF PRENATAL EXPOSURE TO DIOXINS ON CORD SERUM IGE

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Abstract
Prenatal background exposure to dioxins may be associated with immune changes in the fetus. To examine such effects, we considered the effects of prenatal exposure to dioxins on cord serum IgE levels in 232 Japanese neonates. Among dioxin congeners, only 33'4'4'-TCB was significantly positively correlated to cord serum IgE levels (p=0.038). This positive correlation may have occurred by chance and low background exposure to dioxins may not influence the production of IgE in the fetus.
Whether cord serum IgE is a sensitive indicator for atopy prediction in later childhood is controversial, therefore we need to examine the effects exposure to dioxins may have on allergic prevalence in later childhood in this ongoing prospective cohort study.

Introduction
Dioxins are widespread environmental pollutants that have been associated with immunotoxic effects. Developing fetuses may be more susceptible to the effects of environmental chemicals. Data regarding the immunotoxic effects in children is scarce. There has been only one report that demonstrated a relationship between PCB exposure and cord blood IgE.[1] However, this report did not adjust for confounding factors, nor did it exclude the possibility of maternal blood contamination. For the purpose of investigating the effects of prenatal exposure to dioxins on cord serum IgE, we performed a multiple regression analysis in order to adjust for confounding factors, and we checked IgE and IgA in cord blood to rule out the possibility of maternal blood contamination.

Materials and Methods
We recruited pregnant women between July 2002 and July 2004 from the Sapporo Toho Hospital in Hokkaido, Japan (this study became known as the *Hokkaido Study on Environment and Children's Health*). All the subjects were native Japanese and were residents of Sapporo or surrounding areas. The subjects completed a self-administered questionnaire survey after the 2nd trimester during their last pregnancy. The questionnaire provided information relating to their dietary habits, exposure to chemical compounds in their daily life and at work, home environment, smoking, and medical histories for themselves and their partners. Prenatal information regarding the mothers and their children was collected from medical records.
A 40-ml blood sample was taken from the maternal peripheral vein after the 2nd trimester during their last pregnancy. When we were not able to withdraw blood due to anemia during pregnancy, we instead took the sample during hospitalization immediately after delivery. All samples were stored at –80°C until analysis. The concentrations of dioxins in the maternal blood were measured using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS) equipped with a solvent-cut large-volume injection system at Fukuoka Institute of Health and Environmental Sciences.
Cord serum IgE and IgA were determined with the SRL, Inc. Turbidimetric Immunoassay and Enzyme Immunoassay, respectively. In order to avoid the possibility of maternal blood contamination, we regarded any cord serum IgA>10 mg/dl sample as inappropriate.
For the purpose of analyzing samples with dioxin and cord serum IgE measurements below the detection limit, we inputted a value equal to half the detection limit. We performed a multiple regression analysis to examine the association between cord serum IgE and dioxin levels in the mother's blood. For the multiple regression analysis,

the levels of dioxins in the mother's blood and cord serum IgE were logarithmically transformed. The final models adjusted for risk factors associated with the outcomes at p-values<0.10 or risk factors known to be strongly associated with outcomes based on previous literature (mother's age, parental allergic history, smoking during pregnancy, parity, baby's sex, gestational age, family income, frequency of fish consumption, distance of highway to home). When we examined the levels of dioxins among blood sampling time (during pregnancy and after delivery) by the Mann-whitney test, there were significant differences in the levels of some dioxin congeners. Based on these results, sampling time was also adjusted through a multiple regression analysis. Results were considered significant if $p < 0.05$. For analysis we used SPSS 13.0J.

Results and Discussion

234 mother-infant pairs completed the questionnaire, exposure measurements, and cord serum IgE sampling. Two pairs were excluded since their measurements showed IgA>10 mg/dl, suggesting possible maternal blood contamination. In total, 232 mother-infant pairs were included in this study. Cord serum IgE ranged from below the detection limit (0.05 IU/ml) to 10.9 IU/ml. The percentage of samples found to be below the detection limit was 16.4% (n=38). Of the 232 cord serum samples, the geometric mean was 0.257 IU/ml and 16 samples (7.0%) had IgE concentrations above 2.0 IU/ml. Compared with a previous study of 1110 cord blood IgE samples in Japan in which the geometric mean was 0.286 IU/ml and 8.4% had an IgE concentrations above 2.0 IU/ml,[2] we can see that the measurements in our cohort study were similar.

Table 1 shows the results of the multiple regression analysis of the association between the levels of dioxins in the maternal blood and cord serum IgE. This is the first report to investigate the association between maternal blood dioxins and cord serum IgE adjusting for confounding factors. The positive correlations for 33'4'4'-TCB (PCB77) were found to be significant (β =0.329,p=0.038). Reichortova, et al. reported that PCB118 in the placental tissue is positively correlated to cord serum IgE using the Spearman correlation,[1] but our data did not show significant correlation (β =0.211,p=0.376).

Our results also show that this one positive correlation may have occurred by chance. In this study the mean (range) level of PCBs and dioxins in the maternal blood samples was 18.2 (4.0-51.2) pg TEQ/g lipid, lower than that of subjects in other domestic areas.[3] Low background exposure to dioxins may not influence the production of IgE in the fetus.

Whether cord serum IgE is a sensitive indicator for atopy prediction in later childhood is controversial. Therefore, it is hoped that we continue this study to eventually demonstrate the relationship between dioxin exposure and the prevalence of allergic disease.

Acknowledgements

We thank the medical staff at Sapporo Toho Hospital, Higashi-ku, Sapporo for recruitment of the participants. We are also grateful to the participating mothers for their cooperation in providing the data. This study was supported by a Grant-in-Aid for Health Scientific Research from the Japan Ministry of Health, Labor, and Welfare, and by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

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Table1. Adjusted association of dioxins in maternal blood with cord serum IgE (n=232)

	Cord serum IgE		
	β [95%CI]	t	p-Value
PCDDs			
2,3,7,8-TCDD	-0.227[-5.817,0.746]	-1.228	0.221
1,2,3,7,8-PeCDD	-0.162[-0.615,0.292]	-0.703	0.483
1,2,3,4,7,8-HxCDD	-0.248[-0.659,0.163]	-1.187	0.236
1,2,3,6,7,8-HxCDD	-0.257[-0.726,0.211]	-1.084	0.28
1,2,3,7,8,9-HxCDD	-0.063[-0.385,0.259]	-0.383	0.702
1,2,3,4,6,7,8-HpCDD	-0.111[-0.636,0.414]	-0.417	0.677
OCDD	0.277[-0.235,0.788]	1.065	0.288
PCDFs			
2,3,7,8-TCDF	0.244[-0.198,0.687]	1.089	0.277
1,2,3,7,8-PeCDF	0.233[-0.355,0.822]	0.781	0.435
2,3,4,7,8-PeCDF	-0.002[-0.457,0.453]	-0.009	0.993
1,2,3,4,7,8-HxCDF	0.034[-0.328,0.397]	0.187	0.852
1,2,3,6,7,8-HxCDF	-0.202[-0.556,0.152]	-1.126	0.261
2,3,4,6,7,8-HxCDF	-0.032[-1.146,1.083]	-0.056	0.955
1,2,3,7,8,9-HxCDF	ND	ND	ND
1,2,3,4,6,7,8-HpCDF	0.004[-0.279,0.287]	0.03	0.976
1,2,3,4,7,8,9-HpCDF	ND	ND	ND
OCDF	0.151[-1.462,1.763]	0.184	0.854
Non-ortho PCBs			
3,3',4',4'-TCB(77)	0.329[0.018,0.639]	2.084	0.038*
3,4,4',5-TCB(81)	ND	ND	ND
3,3',4,4',5-PeCB(126)	-0.030[-0.337,0.277]	-0.191	0.848
3,3',4,4',5,5'-HxCB(169)	0.158[-0.231,0.548]	0.802	0.424
Mono-ortho PCBs			
2,3,3',4,4'-PeCB(105)[a]	0.190[-0.272,0.652]	0.813	0.418
2,3,4,4',5-PeCB(114)[a]	0.178[-0.355,0.710]	0.659	0.511
2,3',4,4',5-PeCB(118)[a]	0.211[-0.259,0.682]	0.889	0.376
2',3,4,4',5-PeCB(123)[a]	0.263[-0.178,0.704]	1.18	0.24
2,3,3',4,4',5-HxCB(156)[a]	0.297[-0.285,0.879]	1.009	0.315
2,3,3',4,4',5'-HxCB(157)[a]	0.127[-0.439,0.692]	0.443	0.659
2,3',4,4',5,5'-HxCB(167)[a]	0.274[-0.245,0.794]	1.044	0.298
2,3,3',4,4',5,5'-HpCB(189)[a]	0.155[-0.352,0.662]	0.605	0.546
Di-ortho PCBs			
2,2',3,3',4,4',5'-HpCB(170)[a]	0.262[-0.286,0.810]	0.945	0.347
2,2',3,4,4',5,5'-HpCB(180)[a]	0.276[-0.273,0.825]	0.995	0.322
Total			
Total PCDDs	0.243[-0.284,0.769]	0.909	0.364
Total PCDFs	-0.104[-0.753,0.544]	-0.317	0.751
Total PCDDs/PCDFs	-0.200[-0.739,0.339]	-0.732	0.465
Total non-ortho PCBs	0.160[-0.255,0.576]	0.762	0.447
Total mono-ortho PCBs [a]	0.266[-0.262,0.794]	0.997	0.321
Total coplanar PCBs [a]	0.269[-0.260,0.797]	1.006	0.316
Total [a]	0.318[-0.254,0.890]	1.101	0.273
WHO-98			
Total PCDDs TEQ	-0.256[-0.776,0.263]	-0.972	0.332
Total PCDFs TEQ	-0.042[-0.560,0.476]	-0.16	0.873
Total PCDDs/PCDFs TEQ	-0.200[-0.739,0.339]	-0.732	0.465
Total non-ortho PCBs TEQ	-0.025[-0.344,0.294]	-0.154	0.878
Total mono-ortho PCBs TEQ	0.285[-0.287,0.857]	0.986	0.326
Total coplanar PCBs TEQ [a]	0.230[-0.263,0.724]	0.923	0.358
Total TEQ[a]	0.098[-0.539,0.736]	0.306	0.76

ND: non detectable, *p<0.05, a; n=144