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A pilot study for foetal exposure to multiple persistent organic pollutants and the development of infant atopic dermatitis in modern Japanese society

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HIGHLIGHTS

- We measured the accumulation of a wide range of chemical compounds in the umbilical cord tissues.
- Most POPs were not associated with AD at 7 months of age.
- PBDE levels in umbilical cord tissues were associated with the development of infant AD.
- The risk for AD decreased with increasing PBDE concentrations.

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ABSTRACT

Increasing evidence supports that harmful chemicals accumulating in the human body may pose a significant threat to infant health through foetal exposure. Persistent organic pollutants (POPs) are thought to enhance the risk for later development of allergic disease like atopic dermatitis (AD). However, few studies have evaluated the effect of foetal exposure to various POPs on the development of AD in early infancy. Here, we describe the impact of foetal exposure to a number of POPs on the occurrence of AD in 7-month-old infants. The participants were 81 infants with or without AD who participated in a birth cohort study, where the concentrations of 15 polychlorinated biphenyl (PCBs) congeners, dichlorodiphenyltrichloroethane (*p,p'*-DDT), dichlorodiphenyldichloroethylene (*p,p'*-DDE), β -hexachlorocyclohexane (β -HCH), hexachlorobenzene (HCB), *cis*-nonachlor, *trans*-nonachlor, mirex, oxychlorodane, and 27 polybrominated diphenyl ether (PBDEs) congeners were measured in the umbilical cord tissues collected immediately after birth. At 7 months, 27 of the 81 infants (33.8%) were diagnosed with AD. Of all POPs examined, total concentrations of 27 PBDE congeners were associated with a significantly decreased incidence of AD. Notably, the concentration of 27 PBDEs was significantly lower in AD infants than in non-AD infants ($P < 0.01$), and the risk of AD development decreased with increasing PBDE levels. These results suggest that foetal exposure to PBDEs is a possible contributing factor to reducing AD in early infancy.

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1. Introduction

A wide range of harmful chemical compounds detected in the human body is known to pose a serious threat to human health. Among the chemicals, persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs) and polybrominated diphenyls (PBDEs) have received considerable attention from researchers because of their long-term bioaccumulation potential and various

toxicities. The toxic actions extend to disruption in endocrine, reproductive, nervous and even immune systems, resulting in detrimental consequences to their normal functions. So far, there has been much evidence that exposure to PCBs is associated with decreased thyroid hormone levels, altered reproductive hormone levels, impaired spermatogenesis, ovarian dysfunction, and neurodevelopmental disturbance (Grandjean and Landrigan, 2006; Meeker and Hauser, 2010; Sharpe, 2010; Craig et al., 2011; Boas et al., 2012). PCB exposure also could lead to alterations in lymphocyte subsets, modulating immune responses (Kunisue et al., 2006; Glynn et al., 2008; Horvathova et al., 2011; Andra and Makris, 2012). Likewise, accumulated PBDEs, which had been

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used as flame retardants for many household products including electronic equipment, textiles, and furnishings, can exert the similar health-threatening behaviour to PCBs (Clarke and Smith, 2011; Dingemans et al., 2011; Andra and Makris, 2012) and seem to have immune-modulating effects (Lundgren et al., 2009; Hong et al., 2010).

Developmental immunotoxicity induced by the accumulated chemical compounds is a growing health concern since it could lead to the aberrant balanced immune responses, resulting in immune disease such as autoimmune and allergic disease (Chen et al., 2006). It can be assumed that the chemical induced dysregulation of T helper cell responses is an underlying mechanism by which susceptibility to allergic disease is enhanced. In fact, an increasing number of studies suggests that exposure to POPs can be a risk factor for the development of allergic diseases and even perhaps to their onset (Luster et al., 2003). There are continuing reports for PCB exposure in human despite the exposure levels decreasing worldwide, and it is jeopardizing children's health because PCBs cross the placenta into the fetuses (Park et al., 2008). Grandjean et al. (2010) reported that PCB exposure was likely to contribute to the development of asthma in children. There is, on the other hand, evidence showing no relationship between the exposure to harmful chemicals and the development of allergic diseases (Noakes et al., 2006), the causal relationship being controversial. Exposure to PBDEs can also be considered a contributing factor to allergic diseases because of their structural similarity to PCBs, but so far there has been no epidemiological evidence for such health-threatening effects of PBDEs. In addition, given their bioaccumulation potential and chemical similarity, it is likely that other similar agricultural pesticides are potential immune-toxicants and thus to have influence on the development of allergic disease, but no epidemiological study have reported the associations of exposure to the other POPs with the development of allergy.

As with many developed countries an increasing number of infants who present with allergic diseases has been reported in Japan. Among several allergic diseases, the development of atopic dermatitis (AD) in infants is of particular interest because it is often evident within only a few months after birth. Infants with AD are likely to develop severe allergic diseases such as food allergy and asthma during the so-called allergy March (Spergel and Paller, 2003). These facts implicate that AD is a logical target as the earliest presentation of immune dysregulation caused by prenatal exposure to the chemical compounds, highlighting the need to assess its impact. To identify chemical compounds that have the potential risk for AD, we set up a prospective birth cohort study examining the relationship between prenatal exposures to the various chemicals and the development of AD at the age of 7 months. In this study, we measured the concentrations of the chemicals in the umbilical cord tissues to evaluate the prenatal exposure. It is appropriate to use the umbilical cord tissues because they more directly reflect the accumulation of chemicals in fetuses than does cord blood serum (Kawashiro et al., 2008).

2. Materials and methods

2.1. Cohort study

Our prospective birth cohort study at Kawatsutsu-Chiba Hospital in Japan recruited 254 pairs of mother and child. After delivery, baseline characteristics of parents, including data on parental allergic disease, were obtained through questionnaire. The mothers answered a subsequent questionnaire at 1, 4 and 7 months with a main focus on their feeding method and presence or absence of skin rash that last more than 2 months and its distribution. One of the authors (SS) interviewed mothers by telephone about eczema at 7 months in detail and made diagnosis of atopic diagnosis.

All participating mothers provided written informed consent to participate in the study, which was approved by the local ethics committee.

2.2. Sample collection and measurement of chemical compounds

Umbilical cord tissues were collected immediately after birth in the delivery room. The tissues were cut at a distance from 10 to 15 cm from the neonatal umbilicus. After maternal and neonatal blood were wiped off with clean gauze the tissues were stored in glass containers that had been washed with acetone and heat-treated at 400 °C to prevent contamination of other chemicals, then being kept at –80 °C for long-term storage. Eighty-six umbilical cords were selected that were long enough to enable measurement of various chemical compounds (approximately 10 g) and were subject to high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS).

The chemical compounds that were measured are as follow: PCBs (CB-28, 48/47, 74, 99, 118, 138, 146, 153, 156, 163/164, 170, 180, 182/187, 194, and 199); PBDEs (BDE-3, 7, 15, 17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 138, 153, 154, 156, 183, 184, 191, 196, 197, 206, 207, and 209); dichlorodiphenyltrichloroethane (*p,p'*-DDT), dichlorodiphenyldichloroethylene (*p,p'*-DDE), β -hexachlorocyclohexane (β -HCH), hexachlorobenzene (HCB), *cis*-nonachlor, *trans*-nonachlor, mirex, and oxychlordane. The measurements of PBDEs were performed by SRL, Inc. (Tokyo, Japan) and those of PCBs and the other POPs by Shimadzu Techno-Research, Inc. (Kyoto, Japan) in accordance with the procedure as earlier described (Kawashiro et al., 2008). The limit of qualification (LOQ) for PCBs was 0.1 pg/g wet weight and that for PBDEs and the other POPs were 0.2 pg/g wet weight; the measurement values less than the LOQ were set to zero.

2.3. Statistical analysis

Concentrations of chemicals in the umbilical cord were used in the statistical analysis. Several variables were described employing frequencies and proportions for categorical data, and means and standard deviations (SD) for continuous variables. We compared patient characteristics using Fisher's exact test for categorical outcomes and *t*-tests for continuous variables, as deemed appropriate. Since the data of various chemicals did not have a normal distribution, nonparametric tests were used. To evaluate the correlation between chemical concentration and the occurrence of AD, multivariate analysis was performed using the logistic regression model with a step-wise selection procedure. The stepwise procedure was set to a threshold of 0.05 for inclusion and 0.05 for exclusion. In addition, the Akaike Information Criterion (AIC), a measure of the relative quality of fitness in a statistical model, was applied to determine the best model among those tested. A *P*-value of less than 0.05 was employed to indicate statistical significance. All statistical analyses were performed with the use of SPSS program (v. 19.0, SPSS Inc.).

3. Results

3.1. Cohort and basic statistics

To measure the concentrations of POPs, sufficient amounts of umbilical cord tissues were required. Of all umbilical cords collected at delivery, 86 umbilical cords were longer than 25 cm, and these were used for further analyses. The concentrations of all chemicals are summarised in Table 1. With regards to AD diagnosis, only 81 participants were evaluated because of incomplete questionnaires. The number of infants who developed AD at

Table 1

Baseline characteristics of AD and Non-AD groups.

Characteristics	AD (N = 27)	Non-AD (N = 54)	P-value
Baby's sex [boys (%)]	18 (66.7%)	31 (57.4%)	0.477 ^a
Age of mothers [years, mean $\pm$ SD]	32.7 $\pm$ 4.7	31.6 $\pm$ 4.2	0.659 ^b
Gestational age [months, mean $\pm$ SD]	39.3 $\pm$ 1.4	38.6 $\pm$ 1.4	0.034 ^b
Birth weight [g, mean $\pm$ SD]	3053 $\pm$ 388.8	3012 $\pm$ 404.2	0.324 ^c
Maternal allergic history [number (%)]	12 (44.4%)	17 (32.1%)	0.342 ^a
Paternal allergic history [number (%)]	12 (44.4%)	21 (38.9%)	0.640 ^a
Maternal smoking [number (%)]	8 (29.6%)	11 (20.4%)	0.409 ^a
Older siblings [number (%)]	7 (25.9%)	20 (37.0%)	0.328 ^a
Pet ownership [number (%)]	9 (33.3%)	8 (14.8%)	0.081 ^a

^a Statistical analyses were performed with Fisher's exact test.^b Statistical analyses were performed with Mann-Whitney U-test.^c Statistical analyses were performed with t-test.

7 months of age was 27. Baseline characteristics of infants with AD and infants without AD are listed in Table 1. There were no significant differences between the two groups.

3.2. Chemical profile of umbilical cords

15 PCB congeners, 27 PBDE congeners, and the other POPs including *p,p'*-DDT, *p,p'*-DDE, β -HCH, HCB, *cis*-nonachlor, *trans*-nonachlor, mirex, oxychlorane were investigated. The total concentrations of all PCB congeners (Σ PCB-15) and those of 27 PBDE congeners were set to be analysed (Σ PBDE-27). Table 2 summarises the levels of the all POPs detected in the umbilical cord tissues and indicates the percentage of total concentrations of the chemical compounds. All POPs were detected in most of the tissues and the most commonly detected POPs were *p,p'*-DDE, β -HCH, PCBs, and PBDEs. *p,p'*-DDE was found at the highest concentrations, followed by β -HCH, Σ PCB-15, Σ PBDE-27, and HCB, at 122.7 pg/g-wet, 73.33 pg/g-wet, 60.63 pg/g-wet, 55.06 pg/g-wet and 22.89 pg/g-wet, respectively. These accounted for about 90% of all chemical compounds detected in the umbilical cord tissues. The other POPs were found at relatively low levels. In addition, Σ PCB-15 levels were strongly correlated with those of other POPs but not with Σ PBDE-27 (Table 3). We conducted factor analysis for all chemical compounds measured in preparation to subsequent association analysis (Table 4).

3.3. Correlation between POPs and development of AD

Using results from factor analysis, we compared the levels of four chemical compounds, including Σ PCB-15, β -HCH, *trans*-nonachlor, and Σ PBDE-27, in umbilical cords between the 2 groups: the AD group (N = 27) and the non-AD group (N = 54). Interestingly, only Σ PBDE-27 levels were significantly different between the 2 groups, as determined by univariate analysis (Table 5). The concentrations of Σ PBDE-27 were lower in the AD group than the non-AD group ($P = 0.006$, Mann-Whitney test with Bonferroni correction). However, the total IgE levels in cord blood were not correlated with the levels of Σ PBDE-27, PCBs and any other POPs (data not shown). In confirming the relationship between Σ PBDE-27 levels and AD, tertile analysis revealed that the risk for developing AD was decreased in middle levels (odds ratio [OR], 0.263; confidence interval [CI], 0.084–0.821) and high levels of Σ PBDE-27 (OR, 0.136; CI, 0.037–0.501) (Table 6). Besides Σ PBDE-27, no other associations were found between chemical exposure and the development of AD.

4. Discussion

The results of this study showed that the prevalence of AD at 7 month of age might be negatively associated with the summa-

tion of the concentrations of 27 PBDE congeners in umbilical cord but not the sum of the PCB congeners and the other POPs, indicating the potential impact of the foetal exposure to PBDEs for early developing AD in infants. In the present study, AD was diagnosed using a questionnaire and telephone interview and blood examination was not done. Thus it was inconclusive whether the AD developed by the age of 7 months was atopic or non-atopic. However, we consider that this study has important implications as the first study to show an association between fetal exposure to PBDEs and the development of AD in the first few months of life.

Some studies have suggested that PCB has the potential to act as an immune-disruptor to induce the skewing of immune cell population which leads to allergic response (Reichertova et al., 1999; Strenzke et al., 2001; Horvathova et al., 2011). By contrast, Grandjean and his colleagues have shown that children with AD had lower prenatal PCB exposures than did nonallergic children (Grandjean et al., 2010). We failed to observe any correlation between PCB exposure and the development of AD, despite detection of PCBs in all umbilical cords examined. It might be possible that postnatal exposure to PCB have some role in the later development of subsequent allergic diseases. In the present study, however, the clinical endpoint was set up earlier in order to evaluate the impact of intrauterine exposure, and thus we did not examine the effect of breastfeeding, which is an influential postnatal environmental factor as well as intrauterine exposure.

As with PCBs, *p,p'*-DDE (the metabolite of *p,p'*-DDT) and β -HCH were detected at relatively high levels in the umbilical cords. These POPs have been reported to exert adverse immunological effect, possibly skewing the T-cell population ratio into preponderance of T helper (Th) 2 cells, which are critical to the pathogenesis of allergic disease (Daniel et al., 2001, 2002). However, we were not able to identify any associations between *p,p'*-DDT, *p,p'*-DDE, β -HCH, and AD. Likewise, other POPs, including HCB, *cis*-nonachlor, and *trans*-nonachlor, did not influence the development of AD, although these were detected at low levels in umbilical cords and they were not expected to play a major health-threatening role.

Unlike the aforementioned chemical compounds we examined, our results showed that PBDEs might play a preventive role in the onset of AD in early infancy. Given that the concentrations of PBDEs in umbilical cord tissue were not associated with the total IgE levels, they might not be involved in Th1/Th2 unbalance and the aberrant production of IgE but counteract the development of AD through the interference with other certain immune cell interactions resulting in the prevention of AD. This notion could be supported by recent interesting findings. Intriguingly, the activation of Aryl hydrocarbon receptor (AhR) has the important role in the differentiation of T regulatory 1 cell (Tr1 cell) that could suppress the aberrant inflammation caused by allergic reaction (Apetoh et al.,

Table 2

The POPs distribution pattern in the umbilical cord tissues. *p,p'*-DDE; dichlorodiphenyldichloroethylene, β -HCH; β -hexachlorocyclohexane, Σ PCB-15; the summation of 15 PCB congeners, Σ PBDE-27; the summation of 27 PBDE congeners, hexachlorobenzene (HCB), *p,p'*-DDT; dichlorodiphenyltrichloroethane.

	N	Means (pg/g-wet)	Percentage	Cumulative percentage
<i>p,p'</i> -DDE	81	122.7	0.334	0.334
β -HCH	81	73.33	0.200	0.534
Σ PCB-15	81	60.63	0.166	0.700
Σ PBDE-27	81	55.06	0.150	0.850
HCB	81	22.89	0.062	0.912
<i>Trans</i> -nonachlor	81	16.17	0.044	0.956
Oxychlorane	81	8.506	0.023	0.979
<i>p,p'</i> -DDT	81	4.203	0.011	0.991
<i>Cis</i> -nonachlor	81	2.243	0.006	0.997
Mirex	81	1.074	0.003	1.000

Table 3Spearman's rank correlation coefficients between concentrations of Σ PCB-15, Σ PBDE-27 and other POPs.

	<i>p,p'</i> -DDE	β -HCH	Σ PCB-15	Σ PBDE-27	HCB	<i>Trans</i> -nonachlor	Oxychlordane	<i>p,p'</i> -DDT	<i>Cis</i> -Nonachlor	Mirex
<i>p,p'</i> -DDE	1									
β -HCH	0.740**	1								
Σ PCB-15	0.754**	0.681**	1							
Σ PBDE-27	0.079	0.055	0.113	1						
HCB	0.731**	0.872**	0.789**	0.017	1					
<i>Trans</i> -nonachlor	0.663**	0.601**	0.804**	−0.039	0.740**	1				
Oxychlordane	0.699**	0.679**	0.816**	−0.069	0.812**	0.973**	1			
<i>p,p'</i> -DDT	0.739**	0.624**	0.665**	0.047	0.679**	0.629**	0.625**	1		
<i>Cis</i> -nonachlor	0.688**	0.648**	0.853**	−0.024	0.784**	0.950**	0.916**	0.698**	1	
Mirex	0.362	0.389	0.769**	0.075	0.494*	0.559*	0.558*	0.417*	0.607**	1

* $r_s > 0.40$.** $r_s > 0.70$.**Table 4**

Factor analysis for POPs detected in umbilical cord tissues.

	Communality	Factor 1	Factor 2	Factor 3	Factor 4
<i>Trans</i> -nonachlor	1.00	0.99	0.39	0.45	−0.06
Oxychlordane	0.96	0.97	0.53	0.54	−0.03
<i>Cis</i> -nonachlor	0.94	0.96	0.54	0.60	−0.08
Σ PCB-15	0.92	0.52	0.94	0.67	−0.03
<i>p,p'</i> -DDE	0.83	0.43	0.85	0.63	0.42
Mirex	0.61	0.32	0.67	0.33	−0.32
<i>p,p'</i> -DDT	0.60	0.35	0.75	0.50	0.26
HCB	0.57	0.42	0.62	0.73	0.22
β -HCH	0.66	0.58	0.59	0.78	0.26
Σ PBDE-27	0.04	−0.06	0.02	0.04	0.18

2010). Once AhR antagonists bind to the intracellular receptor, the activated AhR compounds are translocated to the nucleus in which they upregulate the expression of IL-10 and IL-21 that are involved in the development of Tr1 cell (Apetoh et al., 2010). Interestingly, PBDEs are one of agonists of AhR and thus they have the ability to activate AhR (Peters et al., 2006). Given that the balance of T helper cell development is skewed to Tr1 cells under the effect of PBDEs, it is hardly surprising that the exposure to PBDEs is correlated with the decreasing incidence of AD.

There is an essential conundrum left behind this study as to why the difference occurred between the outcome of PBDEs exposure and that of PCBs in spite of their structural similarity and their binding ability to AhR. Unfortunately, it is difficult to draw a conclusion of this problem in our study, but arguably PBDEs could affect intracellular signal pathways differently from PCBs although both PBDEs and PCBs signal transduction are mediated by the same receptor, AhR. In fact, the toxicity equivalence varies among them, and several studies have reported that the toxicity of PBDEs are substantially lower compared with that of PCBs (Chen and Bunce, 2003). Further study is required to clarify the difference in immune cell responses to PBDEs and PCBs. Moreover, there are various congeners and isomers of PBDEs and PCBs that have a wide range of toxicity and different each property such as toxicity equivalence quality, bind affinity to AhR, and the ability of transactivation of

Table 5

Comparison of the levels of the representative POPs. Median and interquartile range (IQR) is shown here for each POPs both in AD and control groups.

	AD		Non-AD		<i>P</i> -value ^a
	Median (IQR)	<i>N</i>	Median (IQR)	<i>N</i>	
β -HCH	54.53 (41.85–100.1)	27	51.64 (33.76–90.95)	54	0.806
Σ PCB-15	66.51 (38.10–98.24)	27	57.69 (38.30–66.58)	54	0.685
Σ PBDE-27	41.00 (31.00–56.00)	27	54.50 (43.00–72.00)	54	0.006*
<i>Trans</i> -nonachlor	11.23 (8.216–20.91)	27	12.88 (8.000–20.30)	54	0.916

^a Statistical test were performed with Mann–Whitney *U*-test ($P < 0.05$).**Table 6**Cases of AD according to Σ PBDE-27 tertile category. Logistic regression analysis was done according to the tertile category. Low group, Σ PBDE-27 < 42 pg/g wet weight; Middle group, 42 pg/g wet weight $\leq$ Σ PBDE-27 < 63 pg/g wet weight; High group, 63 pg/g wet weight $\leq$ Σ PBDE-27.

		AD cases [number (%)]	OR ^a	95% CI	<i>P</i> -value
Σ PBDE-27	Low	16 (0.571)	1	1	
	Middle	7 (0.259)	0.263	0.084–0.821	0.022*
	High	4 (0.154)	0.136	0.037–0.501	0.003*

^a OR; adjusted odds ratio, CI; confidence interval.* $P < 0.05$.

downstream target genes. Given these observations, it is possible that either specific congeners or isomers of PBDEs and PCBs, or the combination of them could be associated with unique outcomes of the immunological development. It is of great interest for human health to elucidate how PBDEs interact with neonates' immune system, and to examine the various properties of PBDEs congeners and isomers.

5. Conclusions

It is unlikely that the high levels of any POPs detected in umbilical cord tissues contribute to the development of AD in infants and prenatal exposures to POPs are suspected as risk factors—at least in the population examined herein. In our study, foetal exposure to PBDEs was found to have a significant impact on suppression of AD in early infancy but not PCB and the other POPs exposure. Further studies in wider populations are necessary to produce more precise and generalised data in order to understand the effects of the accumulated POPs on infant's immune system. It seems that a variety of POPs, including PBDEs congeners, isomers and other organic compounds, exert differing immune-modulating effects. In addition, large amounts of data in a epidemiological research are required to validate the impact of foetal POPs exposure combined with other environmental factors such as maternal lifestyles, and to assess the current exposure condition of the mothers and infants, because it has been changing reflecting on the present-day environments in our society.

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