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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, oxychlordane, 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.

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 foetuses (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 foetuses than does cord blood serum (Kawashiro et al., 2008).

2. Materials and methods

2.1. Cohort study

Our prospective birth cohort study at Kawatetsu-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 ant the other POPs by Shimazu 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