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Bisphenol A exposure may increase the risk of development of atopic disorders in children

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ABSTRACT

Background: Little is known about the effect of Bisphenol A (BPA) on atopic disorders.
Objective: To investigated the associations (i) between postnatal BPA exposure and allergic diseases in children; (ii) between BPA and IgE levels for the possible disease pathogenesis; and (iii) gender-based differences.
Methods: A total of 453 children from Childhood Environment and Allergic Diseases Study cohort with urine and blood samples were recruited in Taiwan. Urinary BPA glucoronide (BPAG) levels were measured by UPLC–MS/MS at ages 3 and 6 years. The associations between BPAG levels at different ages and IgE levels and the development of allergic diseases were evaluated by multivariate linear regression and logistic regression. A mediation analysis was also conducted to evaluate how much risk of allergic diseases in relation to BPA exposure is explained by IgE changes.
Results: The BPAG levels at age 3 were positively associated with IgE levels at age 3 (β = 64.85 kU/l per ln-unit increase BPAG level; 95% CI, 14.59–115.11 kU/l). Stratified by gender, BPAG levels at age 3 were positively associated with IgE levels at age 3, particularly in girls (β = 139.23 kU/l; 95% CI, 57.38–221.09 kU/l). Similar results were also found at age 6. Urinary BPAG levels at age 3 were significantly associated with asthma at ages 3 and 6, with OR (95%CI) of 1.29(1.08–1.55) and 1.27(1.04–1.55). We estimated that 70% of the total effect of BPA exposure on asthma is mediated by IgE levels.
Conclusions: BPA exposures were associated with IgE levels and may increase the risk of development of allergic diseases in children particularly in girls.

Introduction

Since asthma is one of the most common disorders among children a fuller understanding of its interaction with environmental exposures is essential. Of particular importance are the effects of chemicals with endocrine disrupting properties on allergic diseases (Bonds and Midoro-Horiuti, 2013). Bisphenol A (BPA), an endocrine disruptor, is a component of polycarbonate plastics and epoxy resins, and is used in products ranging from food and beverage containers to thermal-paper receipts. Children's exposure to BPA is through oral, dermal, and respiratory routes (Wilson et al., 2007; Stahlhut et al., 2009). There is increasing health concern regarding common low-level exposure to BPA among the general population (Vandenberg et al., 2013). While BPA is not bio-accumulative, continuous daily exposure (due to numerous sources) leads to an exposure scenario that reminds to that of persistent and bio-accumulative compounds (Chen et al., 2014). Recent BPA data in NHANES suggest longer than expected half-life and substantial non-food exposure (Stahlhut et al., 2009).

Moreover, BPA has been associated with many adverse health effects, including diabetes, obesity, reproductive disorders, cardiovascular diseases, birth defects, chronic respiratory and immune diseases and breast cancer (Rezg et al., 2014). Murine data suggest that exposure to BPA can reduce levels of regulatory T cells, IFN-r, and IL-10, and increase production of IL-4 and antigen-specific IgE (Yan et al., 2008; Sawai et al., 2003). Peri-natal exposure to BPA has been reported to enhance allergic sensitization and bronchial eosinophilic inflammation and responsiveness in a

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susceptible animal model of asthma (Midoro-Horiuti et al., 2010). However, whether these findings in rodent models are applicable to human subjects remains an open question.

Currently, few studies have examined the association between environmental BPA and allergic diseases in children. For years, human data on the association between BPA exposure and asthma-related outcomes have been limited to case reports of occupational asthma among workers exposed to epoxy resins (Hannu et al., 2009; Kwak et al., 2009). Prenatal BPA exposure has been reported to increase the odds of childhood wheezing while pre-natal and post-natal exposure has been reported to be associated with asthma development (Spanier et al., 2012; Wang and Lin, 2015; Donohue et al., 2013; Gascon et al., 2015). However, the underlying mechanisms for BPA-induced asthma remain to be elucidated. There is a paucity of data on the role of BPA exposure in development of other allergic diseases such as atopic dermatitis (AD) and allergic rhinitis. Moreover, little is known about whether there is any gender difference in these associations.

Since young children are more vulnerable to toxic chemicals due to the immaturity of their organs and increased dosage per unit body surface area, this study was conducted to evaluate (i) the association between postnatal BPA exposure and allergic diseases in pre-school children; (ii) the association between postnatal BPA and IgE levels for the possible disease pathogenesis; and (iii) gender-based differences, if any, in these associations.

Methods

Study population

A total of 453 kindergarten children from Childhood Environment and Allergic Diseases Study (CEAS) cohort with urine and blood specimens were recruited in Taiwan (Wang and Lin, 2015). The concentrations of urinary BPA glucuronide (BPAG) were measured at ages 3 and 6 years as an indicator of exposure and serum total IgE levels were determined as an indicator of sensitization. Data on the children's allergic diseases were collected at ages 3 and 6 years. The association of BPAG levels of children at age 3 with allergic diseases at ages 3 and 6 years and the association of BPAG levels at age 6 with allergic diseases at age 6 year were evaluated. Written informed consent was obtained from all of the parents. The hospital's Institutional Review Board approved the study protocol, which complied with the principles of the Helsinki Declaration.

Questionnaire survey

At ages 3 and 6 years, an International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used for collecting data on the children's allergic symptoms and information on duration of breast feeding, number of older siblings, furry pets, carpets, or incensing at home, fungi at house walls, and tobacco smoke exposure were collected. The parents also answered a standardized questionnaire for basic demographics, birth history, parental history of allergic diseases, and family income.

Allergic diseases

At outpatient clinics in the regional hospitals, experienced pediatric allergists performed a standardized history and clinical examination of participants with a parental-reported doctor-diagnosed AD, allergic rhinitis, and asthma from the ISAAC questionnaire. The cases with AD were further confirmed according to the diagnostic criteria developed by Hanifin and Rajka (1980), while allergic rhinitis was further confirmed using the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (Brozek et al., 2010). Asthma was determined by pediatric allergists based at least on one of the following three criteria: (i) recurrence of at least two of the three symptoms: cough, wheeze, and shortness of breath within the previous 12 months without having a cold (ii) doctor's diagnosis of asthma with ongoing treatment (iii) response to treatment with β2-agonists or inhaled corticosteroids (Soto-Martinez et al., 2009).

Laboratory methods

Urine analyses

The first mid-stream urine in the morning provided by the children at 3 and 6 years of age were stored at −20 °C until analysis. The urine samples were processed by solid-phase extraction. BPAG levels were determined by using ultra-performance liquid chromatography/tandem mass spectrometry (UPLC–MS/MS) with isotope-dilution techniques, as described elsewhere (Zhou et al., 2014). The limit of detection (LOD) was 1.61 ng/ml. For concentrations below the detection limit, a value of half the limit of detection was assigned. All results involved duplicate analysis. Urine creatinine levels were analyzed by enzymatic assay (Cayman Chemical, Ann Arbor, MI, USA) (Cayman Chemical Company, 2012). All statistical models were adjusted for urine creatinine levels.

Total IgE analysis

Serum total IgE levels at ages 3 and 6 years were determined using the Pharmacia UniCap IgE assay test system according to the manufacturer's prescribed protocol (Pharmacia Diagnostics, Uppsala, Sweden). Total IgE levels were considered increased at values of greater than 100 kU/l (Weidinger et al., 2006). Concentrations below 0.35 kU/l were defined as undetectable IgE.

Statistical analysis

The relationships between urine BPAG and IgE levels were analyzed by linear regression. For data with skewed distributions, they were log (Ln)-transformed before further analyses. All log-transformed data in the study had a normal distribution and no significant outliers were found. The associations between urine BPAG and allergic diseases were analyzed by univariate and multivariate logistic regression. Potential confounders from a review of the literature, including gender, gestational age, parity, maternal age, education, occupation, diets and supplements during pregnancy, family income, parental atopy, duration of breast feeding, tobacco smoke exposure, incensing and carpets at home, and fungi on house walls were all taken into consideration. Only those potential confounders with a 10% change in point estimate of the crude model were included in the final model. All hypothesis testing was two-sided and statistical significance was set at $p < 0.05$. All analyses were performed using the SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

To evaluate how much risk of asthma in relation to exposure to BPA was explained by changes in IgE, we conducted a mediation analysis (Ditlevsen et al., 2005). The mediation analyses incorporated the different regression coefficients (exposure: BPA, mediator: IgE, and outcome: asthma). The mediation proportions, the percentage change of the regression coefficients when we included an intermediate variable in the model, were calculated (Supplemental material, Fig. S1). Both logistic and linear regressions were used.

Results

At age 3 years, we included 453 children with all the information required. At age 6 years, after excluding children due to lost to