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Association between organophosphorus flame retardant exposure and precocious puberty in girls

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Pediatric

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□ Abstract □

Objective: To investigate the association between organophosphorus flame retardant exposure and precocious puberty in girls.

Methods: A total of 60 girls with precocious puberty who were admitted to the Department of Pediatric Endocrinology, Lianyungang Clinical Medical College of Nanjing Medical University from February 2023 to February 2024 were selected as the study subjects, and 40 healthy girls who were admitted to the same hospital during the same period were selected as the control group. A self-designed questionnaire was used to investigate the socio-demographic characteristics and lifestyle of the study subjects. Ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was used to detect the concentrations of 13 organophosphorus flame retardants in urine. Including diisobutyl phthalate (DIBP), din-butyl phthalate (DNBP), di (2-propyl heptyl) phthalate [DPHP], bis (2-butoxyethyl) phthalate (BBOEP), dioctyl cyclohexyl phthalate (DOCP), dimethyl phthalate (DMCP), bis (2-ethylhexyl) phosphate. Esters (BEHP), dimethyl phthalate (DMP), methylthiophosphatidyl diamine (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phthalate (DEP), diethyl thiophosphate (DETP), diethyl dithiophosphate (DEDTP). Logsitic regression model was used to analyze the association between organophosphorus flame retardants exposure and precocious puberty in girls.

Results: The detection rates of DPHP, BEHP, DMP, DMTP, DEP, and DETP in girls' urine were all higher than 50%, and DEP and DETP had the highest detection rates (100%). The results of binary Logistic regression model showed that BEHP exposure might increase the risk of precocious puberty in girls (*OR*=2.291, *95%CI*: 1.010-8.445).

Conclusions: Exposure to BEHP increases the risk of precocious puberty in girls, which may be a risk factor for precocious puberty.

Key words: Precocious puberty, Organophosphorus flame retardants, Endocrine-disrupting chemicals, Lifestyle

Organophosphorus Flame Retardants (OPFRs) are additive organic flame retardants with both plasticization and lubrication functions. They have replaced the dominant position of brominated flame retardants due to their good flame retardancy, environmental protection, compatibility, low corrosion, safety and low cost. They are widely used in the production of building materials, plastic products, home decoration, children's toys, electronic products and textiles. [1]OPFRs are added to products by direct addition rather than chemical bonding, so they may be released into the environment due to volatilization, leaching and wear. [2]Humans are exposed to OPFRs through air, dust inhalation, food intake, skin contact, and other pathways. Previous studies have shown that OPFRs and its metabolites can be detected in nails, hair, serum, urine, and breast milk. [3]The widespread application of OP[4]FRs has caused serious harm to the ecological environment and human health. Toxicological studies have found that OPFRs have a variety of toxic effects, such as neurotoxicity, endocrine disturbance and reproductive development.

Precocious puberty refers to the appearance of pubertal development signs before a specific age limit. The specific age definition varies by country and region. In China, it usually refers to breast development before 7.5 years old for girls or menarche before 10.0 years old for girls, and testicular enlargement[5] before 9.0 years old for boys. The incidence of precocious puberty is on the rise both at home and abroad, which has gradually become a global public health problem[6-8]. Early sexual development is associated with impaired adult height, anxiety, depression and other psychosocial problems in children, and may also increase the risk of diabetes, reproductive system malignant tumors, and cardiovascular diseases[6] in adulthood. The etiology of precocious puberty is complex, involving many factors[9] such as genetics, environment, nutritional status and endocrine regulation.

With the progress of society and the development of industrial production, environmental endocrine disrupting substances (EDCs) have been regarded as important factors affecting human health. Bisphenol A, phthalates, polychlorinated biphenyls and polycyclic aromatic hydrocarbons (pahs) can mimic or interfere with the normal function of sex hormones and promote the occurrence[10] of precocious puberty. Animal experiments have shown that OPFRs have estrogen-like effects[11] and potential Hypothalamic-Pituitary-Gonadal Axis (HPGA) regulation[12], which is related to the process of sexual development. The purpose of this study is to explore the relationship between environmental exposure to organophosphorus flame retardant (OPfrs) and precocious puberty by detecting the concentration of organophosphorus flame retardant (OPfrs) in urine, so as to encourage relevant departments to strengthen environmental protection and food supervision, which is of great significance to reduce the incidence of precocious puberty and promote physical and mental health of children and adolescents.

1 Subjects and Methods of study

1.1 Study Subjects

A total of 60 girls with precocious puberty admitted to the Department of Pediatric Endocrinology, Lianyungang Clinical Medical College of Nanjing Medical University from February 2023 to February 2024 were selected as the study subjects, and 40 healthy girls who underwent physical examination during the same period were selected as the control group. This study was approved by the Ethics Committee of the First People's Hospital of Lianyungang. Ethics number: KY-20231204001-01.

Inclusion criteria:

(1) Early appearance of sexual characteristics: girls had breast development before 7.5 years old or menarche before 10 years old;

(2) Enlarged gonads, that is, enlarged uterine and ovarian volumes and multiple ovaries with diameters ≥4cm could be seen in the ovaries by pelvic ultrasound;

(3) macropubertal levels of serum gonadotrophins and sex hormones;

(4) advanced bone age (≥1 year beyond chronological age);

(5) The annual growth rate was higher than that of healthy children of the same age.

(6) no treatment with gonadotropin-releasing hormone analogue.

2.2. Exclusion Criteria:

(1) combined with liver, kidney, thyroid, adrenal insufficiency or other systemic chronic diseases;

(2) definite history of radiotherapy and chemotherapy;

(3) taking drugs that may affect the hypothalamic-pituitary-gonadal axis before the visit;

(4) Peripheral precocious puberty caused by organic diseases such as congenital adrenal hyperplasia, McCune-Albright syndrome and ovarian tumors.

1.2 Research methods

1.2.1 Questionnaire survey On the basis of consulting a large number of domestic and foreign related literature to understand the current status and progress of the research on precocious puberty, a questionnaire was designed according to the purpose of this study (see the Appendix). The questionnaire was used to investigate the family factors and lifestyle of the subjects, including birth weight, time of outdoor activities per day, time of sleep per day, time of electronic device use per day, whether to sleep with the light on, whether to use adult cosmetics, eating fried and high-calorie food, whether to use health care products or supplements, mother's menarche age < 13 years, and residence. A voluntary questionnaire was used to investigate the girls' socio-demographic characteristics and lifestyle, and the investigators explained the purpose and procedure of the survey in detail, and avoided any inductive language.

1.2.2 Determination of OPFRs metabolites in urine ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS, Agilent LC/MS 6490 mass spectrometer) was used to detect the concentrations of 13 OPRFs metabolites in girls' urine. The OPrfs metabolites included Disobutyl Phthalate (DIBP), di-n-butyl Phthalate (DNBP), Di(2-propylheptyl) phthalate (Di(2-propylheptyl) phthalate), and dibutyl phthalate (di (2-propylheptyl) phthalate). DPHP], Bis(2-butoxyethyl) Phosphate (BBOEP), Di-octyl Cyclohexyl Phthalate (DNBP), di-octyl cyclohexyl phthalate (DPHP), di-octyl cyclohexyl phthalate (DPHP), di-octyl cyclohexyl phthalate (BBOEP), di-octyl cyclohexyl phthalate (DPHP). DOCP), Dimethyl Phthalate (DMCP), Bis(2-ethylexyl) phosphate (BEHP), di-octyl cyclohexyl Phthalate (Dimethyl Phthalate, DMP), Dimethyl Thiophosphoryl (DMTP), Dimethyl Dithiophosphate (DMDTP), Diethyl Phthalate (DMDTP), DEP), Diethyl Thiophosphate (DETP), Diethyl Dithiophosphate (DEDTP). The detection method has been published in the literature [16], and the brief steps are as follows: Then 20 μL of mixed

internal standard (500 ng/mL) and 1 mL ammonium acetate buffer solution (10 mmol/L) were added. After shaking and mixing, the mixture was processed by solid phase extraction. After centrifugation and concentration, 200 μL of methanol water (1: 1) Redissolve, and after centrifugation, 100 μL of supernatant was taken for machine detection. Two low-concentration artificial urine blank samples, one low-concentration quality control sample (1 ng/mL) and one high-concentration quality control sample (10 ng/mL) were set for every 20 samples. The sample recovery rate was 70%-130%, the inter-day and intra-day relative standard deviation was < 15%, and the standard curve R2 was >0.99. The limits of detection of DIBP, DNBP, DBHP, BBOEP, DoCP, DmCP, BEHP, DMP, DMTP, DMDTP, DEP, DETP and DEDTP were calculated. LODs) were 0.067, 0.092, 0.059, 0.273, 0.022, 0.041, 0.144, 0.869, 0.582, 0.464, 0.164, 0.117 and 0.583 ng/mL, respectively.

1.3 Data analysis SPSS27.0 was used for statistical analysis. Non-normally distributed continuous variables were described by median (P25, P75), and Mann-Whitney U test was used to compare the differences between groups. Categorical variables were described by the number of cases, and $\chi 2$ test was used to compare the differences between groups. The values of OPFRs metabolite concentration < LOD in urine were replaced by LOD/√2. OPFRs (DPHP, BEHP, DMP, DETP) with detected concentrations > 50% and differences between groups were included in the binary Logistic regression model after natural logarithm transformation. The final covariates included: time of outdoor activities per day, use of adult cosmetics, frequency of using high-calorie fried food, and maternal age at menarche < 13 years old.

2 Results

2.1 Sociodemographic characteristics and lifestyle

There were significant differences between the girls in the precocity group and the healthy control group in the time of outdoor activities per day, the frequency of using adult cosmetics, the frequency of using high-calorie fried food, and the age of mother's menarche before 13 years old ($P < 0.05$). See Table 1 for details.

Table 1 Sociodemographic characteristics and lifestyle of girls

Variables	Precocious group (n=60)	Healthy control group (n=40)	*chi-square*	P-value
Birth weight				
< 2.5kg	9	8	1.593	0.451
2.5 4 kg	36	26		
> 4kg	15	6		
Mode of delivery				
Term birth was natural	46	30	0.384	0.825
Cesarean section at term	10	6		
Preterm birth	4	4		
Feeding patterns during infancy				
Breastfeeding	42	28	1.316	0.251
Formula feeding	18	12		
Whether you are an only child				
is	33	25	0.554	0.457
no	27	15		
Literacy age				
≤4 years old	17	8	0.889	0.346
> 4 years old	43	32		
Time spent outdoors per day				
< 2 hours	32	11	6.535	0.011
≥2 hours	28	29		
Duration of sleep per day				
< 8 hours	14	10	0.228	0.892
8-10 hours	40	25		
> 10 hours	6	5		
> 10 hours of daily device use				
< 30 minutes	8	6	0.521	0.771
30 minute-1 hour	33	24		
> 1 hour	19	10		
Whether to sleep with the lights on				
is	20	28	0.123	0.726
no	40	12		
Whether to use adult makeup				
is	17	7	3.285	0.07
no	43	33		

Continuation Table 1 Sociodemographic characteristics and lifestyle of girls

Influencing Factors	Experimental group	Control group	chi-square	P-value
Consuming fried, high-calorie foods				
3-4 times/week	19	5	9.823	0.007
1-2 times/week	31	18		
Rarely eaten	10	17		
Whether to use health products, supplements				
is	10	5	0.327	0.568
no	50	35		
Maternal age at menarche < 13 years				
is	22	14	7.719	0.005
no	38	26		
Place of residence				
City	37	22	0.441	0.507
Rural	23	18		
Education level of father				
Junior high school or below	13	9	0.028	0.986
High school	25	16		
College and above	22	15		
Mother's education				
Junior high school and below	10	10	1.307	0.520
High school	28	15		
College and above	22	15		
Annual household income				
< 50,000 yuan	3	2	0.529	0.767
50,000 to 100,000 yuan	19	10		
> 100,000 yuan	38	28		

2.2 Distribution of OPFRs metabolites in urine of girls

Among the 13 OPFRs included in the study, the detection concentration of 6 OPfrs was greater than 50%, including DPHP (53%), BEHP (91%), DMP (83%), DMTP (71%), DEP (100%) and DETP (100%). The concentrations of BEHP, DMP, and DETP in the precocity group were higher than those in the healthy control group, and the concentration of DPHP was lower than that in the healthy control group, and the difference was statistically significant ($P < 0.05$). There was no significant difference in DEP concentration distribution between the two groups ($P > 0.05$). The detection rate of DEDTP was 0, which was not included in the analysis. See Table 2 for details.

Table 2 Distribution of urinary OPFRs metabolites in girls

OPFRs	Detection rate (%)	Precocious group (n=60)			Healthy control group (n=40)			*Z score*	*P*
		P_{25}	P_{50}	P_{75}	P_{25}	P_{50}	P_{75}		
DIBP	15	0.047	0.047	0.047	0.047	0.047	0.047	-0.487	0.626
DNBP	27	0.029	0.029	0.042	0.029	0.029	0.042	-0.189	0.850
DPHP	53	0.042	0.162	0.535	0.042	0.042	0.207	-2.081	0.037
BBOEP	20	0.193	0.193	0.193	0.193	0.193	0.193	-0.280	0.780
DOCP	4	0.016	0.016	0.016	0.016	0.016	0.016	-0.414	0.679
DMCP	27	0.029	0.029	0.042	0.029	0.029	0.042	-0.189	0.850
BEHP	91	1.365	2.844	5.029	0.942	1.578	3.271	-2.449	0.014
DMP	83	0.142	0.178	0.239	0.105	0.128	0.158	-3.240	0.001
DMTP	71	0.412	0.859	2.045	0.412	0.743	1.102	-1.254	0.210
DMDTP	10	0.328	0.328	0.328	0.328	0.328	0.328	-2.115	0.034
DEP	100	1.130	1.939	3.868	1.309	1.731	2.632	-0.739	0.46
DETP	100	0.461	0.777	1.779	0.338	0.556	1.091	-2.146	0.032

2.3 Association between OPFRs single exposure and precocious puberty in girls

After adjusting for the confounding factors of time spent outdoors, use of adult cosmetics, use of high-calorie fried food, and mother's age < 13 years, OPFRs with a detection concentration > 50% and a difference in concentration between groups were included in the Logistic regression model. The results showed that BEHP exposure might increase the risk of precocious puberty in girls (*OR*=2.291, *95%CI*: 1.010-8.445).

Table 3 Binary Logistic regression analysis of influencing precocious puberty

OPFRs	*OR*	*95%CI*	*P*
DPHP	1.943	(0.786, 4.803)	0.150
BEHP	2.291	(1.010, 8.445)	0.048

DMP	2.473	(0.643, 9.229)	0.150
DETP	1.943	(0.786, 4.803)	0.150

3 Discuss

In this study, the correlation between OPFRs and precocity was explored by using Logistic regression analysis based on the detection of OPFRs metabolites in urine and sociodemographic and lifestyle survey in girls. The results showed that BEHP exposure was associated with an increased risk of precocity in girls.

The use of OPFRs has been increasing year by year. The levels of OPFR metabolites in human urine range from 0.083 ng/mL to 65.9 ng/mL, and the global median concentration is 2.93 ng/mL[13]. Diphenylphosphine Hydroxide (DPHP), Bis(chloroisopropyl) Phosphate, BCIPP and Bis(2-chloroethyl) Phosphate (BCEP) are the main components of OPFRs metabolites. Specifically, DPHP was the major OPFR metabolite in Australia, the United States, and Canada, accounting for 86%, 45%, and 86%[14] of the total OPFR metabolites, respectively. However, there are few studies on the characteristics of OPFR exposure and its health risks in Chinese population. A study from Guangzhou showed that OPFRs were common in humans, with a detection rate of up to 70%. The main monomer compound was BCEP, and the concentration was 4.51ng/ml. The living and working environment have an important impact[15] on human exposure. The study by Yu Wang et al. measured 19 OP triesters and 11 diester degradation products in indoor and outdoor dusts collected in China. The estimated daily intake of ∑OP diesters from dust was 0.21ng/kg/ day for adults and 2.59ng/kg/ day for children, indicating that children are more severely[16] exposed to OPfrs than adults. A total of 180 urine samples were collected from people (including adults and children) in western Shanghai, China, and nine OPFRs metabolites were measured. The total urine concentration ranged from 100 to 23800pg/mL, with an average of 1450pg/mL. Increasing age was associated with a significant decrease[17] in urinary OPFRs concentrations.

OPFRs are considered to be one of the environmental endocrine disrupting chemicals (EDCs) with estrogen-like effects, which can disturb hormone balance and interfere with the normal endocrine system function[18] by simulating, enhancing or antagonizing hormone effects. Animal experiments have shown that TPHP and TDCIPP, as typical aryl organophosphatide flame retardants (OPFR), affect the hypothalamic-pituitary-gonadal axis of zebrafish, resulting in changes in 17β-

estradiol and testosterone (T) levels, and a significant increase[19] in the level of vitellinogen (VTG). Exposure of zebrafish embryos to low concentrations (0, 4, 20 and 100μg/L) of TDCPP from 2 h post fertilization to sexual maturity significantly increased plasma estradiol and testosterone levels in female zebrafish. In addition, hepatic vitellogenin (vtg1 and vtg3) expression was upregulated in both female and male zebrafish, indicating that TDCPP has estrogenic[20] activity. In addition, cross-sectional studies based on 2013-2014 National Health and Nutrition Examination Survey (NHANES) cohort data have shown that exposure to organophosphorus flame retardant agents (OPFRs) may be associated[21] with elevated serum sex hormone levels in women, including children, adolescents, and adults. The hypothalamic-pituitary-gonadal axis plays a major role in the regulation of female reproductive development by regulating the production and release of sex hormones, thereby affecting the development of the reproductive system, fertility, and the emergence of secondary sexual characteristics. Sex hormones E2 and P and gonadotrophins FSH and LH are the main hormones to maintain the normal function of the female reproductive system. The dynamic balance between them is regulated by HPOA. Therefore, OPFRs may play an estrogen-like role by increasing the activity of aromatase and increasing the sensitivity of estrogen, leading to the increase of endogenous estrogen secretion, and thus causing precocious puberty.

The molecular mechanism of OPFRs inducing estrogen interference is complex. One of the classical genomic pathways is the interaction between Endocrine-disrupting chemicals and estrogen receptor α (ERα) to recruit coactivators and promote the transcription[22] of target genes. In the two-hybrid yeast assay, TiBP, TPhP, DPK, MDPP, CDP and IPPDP showed antagonistic activities against ERα, indicating that they did not induce the interaction between ERα and GRIP1, but competed with E2 for binding to ERα-LBD. However, the results of the MVLN cell assay indicate that among the six OPfrs, TPhP is the only one that induces estrogenic activity. TPhP acts as an ERα agonist to activate ERE transcription but does not interact[23] with GRIP1. The mechanisms leading to the estrogenic effects of OPFR are complex, and further studies are needed to investigate not only the effects of OPFR on ER, but also the non-receptor-mediated pathways of E_2 metabolism and transformation induced by OPFR.

Although organophosphate flame retardants (OPFRs) may interfere with the timing of hypothalamic-pituitary-gonadal axis activation by simulating the physiological effects of endogenous estrogen, their effects on the progression of puberty and the related molecular

mechanisms have not been fully elucidated. In a cohort study conducted in Europe, BEHP and Diisononyl phthalate (DiNP) metabolites were associated with slightly higher odds of the onset of puberty in boys, with stronger[24] associations with DiNP concentrations in boys who were overweight or obese. The study by Carmen Freire et al. also found that prenatal exposure to BEHP may increase the risk[25] of puberty and premature gonadal development in Spanish boys. Animal experiments provide a molecular mechanism for the reproductive and developmental toxicity of BEHP. Studies have shown that BEHP can up-regulate the IGF-1/PI3K/Akt/mTOR pathway and GnRH expression in the hypothalamus of adolescent female rats, increase the levels of IGF-1 and GnRH in the serum and hypothalamus[26], and lead to the initiation of female sexual development. However, the evidence for an association between OPFRs exposure and the onset of precocious puberty is inconsistent. Ikeda's study concluded that OPFRs mixtures were not significantly associated with early or delayed puberty, except for slightly delayed menses in girls. [27]Cohort studies from Russia[28] also suggested no association between urinary concentrations of BEHP and pubertal progression in boys.

Although this study provides preliminary evidence of an association between OPfrs and sexual development, there are still some limitations. First, the short half-life of organophosphorus flame retardants makes it difficult for a single urine test to accurately reflect the long-term exposure level of children. Second, the sample size of this study is relatively small, which may limit the statistical power and generalizability of the results. The lack of urine creatinine correction in this study is insufficient. Urine creatinine correction should be performed first in future related studies to reduce false positive or false negative associations. In addition, long-term follow-up was not available to assess the cumulative effect of OPFRs exposure and its potential long-term effects on sexual development. Long-term follow-up studies will be helpful to reveal the potential cumulative effect of OPFRs exposure on sexual development and its long-term health impact.

4 Summary

This study examined the association between urinary OPFRs concentration and precocity in girls, and Logistic regression analysis showed that BEHP exposure was associated with an increased risk of precocity in girls. This will promote the relevant departments to carry out environmental management legislation and implementation, and strongly support the research and development of green flame retardants, so as to control from the source, which is conducive to better prevention and

control of precocious puberty. Given the limited and conflicting data on the effects of OPFRs exposure on puberty, as well as the widespread exposure in children, large-scale prospective studies are warranted to elucidate their role and specific mechanisms in the temporal variation of puberty.

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