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Original Article

The Risk Factors of Puberty Precocious in Girls: Is the Condition Related with Polychlorobiphenyls?

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ABSTRACT

Aim: Our aim was investigate the effect of polychlorobifenyls (PCBs) and other factors on puberty precocious (PP) in girls were diagnosed with idiopatic PP and premature thelarche (PT).

Materials and Methods: The study group included 50 girls aged between 2-8 years old with PP and PT. The control group included 50 healthy girls with same age range and no puberty findings. Data was collected in terms of breast and pubic hair stages, weight, height, body mass index (BMI), standard deviation scores (SDSs), location of residence, gestational age and maternal age at menarche (AAM). Twenty-one PCB levels were evaluated in serum and urine. One-Way ANOVA test was used for comparison between the groups. For subgroup analysis, Mann-Whitney U test, multiple regression analysis were used.

Results: The mean age of the study and control groups were 6.70±1.20 and 5.23±1.25 years, respectively. The studied PCBs were not detectable found in either the study or the control groups. The BMI SDSs of the patients in study and healthy groups were 0.49±1.09 and -0.12±1.28, respectively (p=0.1). Weight SDSs in the study group were found to be significantly higher than healthy group (0.72±1.35 vs -0.20±1.47, p=0.008 Maternal AAM of the patients in study group was significantly lower (p=0.006). In study group 98% of the patients were living in down town and district, whereas this ratio was 92% in control group (p=0.024). In study group 29 patients (58%) were diagnosed with PT. Basal follicle stimulating hormone and estradiol levels, bone age and uterine longest axis dimensions results were significantly different.

Conclusion: We found that studied PCBs don't influence on PP in girls aged between 2-8 years old. However, weight SDS, maternal AAM, location of residence of the patients had a significant role on PP in this patient population.

Keywords: Puberty precocious, premature thelarche, environmental endocrine distrubs, polychlorobifenyl, obesity

Introduction

Over the last century, it has been seen that the age of onset of puberty has tended to shift earlier. Sorensen et al. (1) have argued that the age of onset of breast development in America has shifted earlier. Central precocious puberty (CPP) occurs as a result of the early activation of the hypothalamus-pituitary-gonad axis and is characterized by the development of secondary sex characteristics in girls before the age of eight (2). Although it is thought that there are many reasons for this, genetic factors, nutritional differences, ethnic origin, environmental factors, and exposure to endocrine disruptors are among the common causes (3,4).

Endocrine disruptors, being one of the causes of CPP, can alter the production, transport, destruction and excretion

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of endogenous hormones and even alter their effects on the target cell. One or more of these effects may also occur together. Exposure can occur transplactentally during the prenatal period, with breast milk in infancy, through inhalation and digestion in childhood, or due to industrial accidents (5). Polychlorinated biphenyls (PCBs), being one of these chemicals, are theoretically constituted of 209 different types of chemical and aromatic compounds that are formed by binding different numbers of chlorine ions in different configurations on a biphenyl structure. They can also be found in synthetic and industrial products. PCBs have been used as organic diluents, softeners, pesticide extenders, adhesives, dust reducers, cutting oils, flame retardants, heat transfer fluids, dielectric fluids for transformers and capacitors, hydraulic lubricants, sealants and in carbonless copy paper. A significant portion of the environmental burden of these compounds is due to careless disposal practices, accidents, leakage from various industrial plants, and chemical waste disposal sites (6). Most of these compounds are lipophilic and have a long half-life. As a result, they accumulate in adipose tissue in living creatures and long-term exposure, even at low levels, may cause chronic toxicity (7). As humans rank high in the food chain at the trophic level, they accumulate high concentrations of these pollutants in lipid tissues and may become more vulnerable to their toxic effects (8).

The main purpose of this study was to analyse the effect of twenty PCB groups, namely; PCB 8, PCB 20, PCB 28, PCB 35, PCB 52, PCB 77, PCB 81, PCB 101, PCB 105, PCB 114, PCB 118, PCB 123, PCB 126, PCB 138, PCB 153, PCB 156, PCB 157, PCB 167, PCB 169 and PCB 189 on PP in girls with the diagnosis of PP or premature thelarche (PT) in our Paediatric Endocrinology Outpatient Clinic. Furthermore, the relationship between PP and the other possible factors such as weight, height, body mass index (BMI), gestational age at birth and maternal age at menarche (AAM) and the residence location of the patients were investigated.

Materials and Methods

The study was conducted after approval was given by the Ethics committee of Ege University Faculty of Medicine (date: 29.12.2015, approval no: 15-11/4).

The study group (group 1) included 50 girls aged between 2 and 8 years old with a diagnosis of idiopathic PP or isolated PT in a single Paediatric Endocrinology Outpatient Clinic. The control group (group 2) included 50 healthy girls with the same age range in the same centre who were admitted to the same department for their routine check-ups and had previously had no chronic disease or evidence of puberty signs.

In the investigation of patients with precocious puberty, their anthropometric measurements and clinicodemographic characteristics were evaluated, and the Tanner stages of the patients were identified. Serum and urine samples were obtained from each patient in order to determine PCB levels. Bone age (BA) (according to the Greulich-Pyle BA atlas), ovarian and uterus sizes, morning basal luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) serum levels were recorded from the files of the patients in group 1. In pelvic ultrasonographic imaging of the patients, cases with ovaries whose longest axis was 2.5 cm or 1 cm^3 in volume from the ovarian dimensions were accepted as being in adolescence, cases with a long axis exceeding 3.4 cm from the uterine dimensions or with an endometrial echo exceeding 2 mm were accepted as being in adolescence (9). Basal FSH, LH, E2 levels were measured in the serum sample by electrochemiluminescence immunoassay method using Roche Diagnostic GmbH (Germany) kits in a Modular Analytics E170- Roche Diagnostic GmbH (Germany) device. In these kits, measurement ranges are given as 0.01-200 mIU/mL for LH and FSH and 5.0-4,300 pg/mL for E2. Basal LH values >0.6 mIU/mL were accepted as true PP. Basal E2 levels above 12 pg/mL were considered higher than the age group (10). Those patients with isolated PT had glandular breast tissue on palpation (as opposed to lipomastia). Their BA corresponded with their chronological age, basal and GnRH-stimulated gonadotropin levels were normal and other signs of puberty such as pubarche and menarche were absent in contrast to those patients with precocious puberty.

Both groups were assessed based on the patients' gestational ages, and location of residence. Preterm birth was determined as being born before the 37th week, and term-birth was determined as having a birth age between 37 and 40 weeks. The location of residence was classified as urban or rural. Maternal AAM, mean BMI and mean weight standard deviation scores (SDSs) of the groups were also compared.

Serum and urine samples of all patients included in the study were stored at -80 °C until they were analysed. Serum and urine PCB measurements were made at Ege University Drug Development and Pharmacokinetics Research Application Centre. For PCB analysis, serum samples were studied by the gas chromatography mass spectrometry (GC-MS) method on a Shimadzu GC-MS QP-2010 Plus (Japan) device. Restek CL Pesticides 2 (20 m, 0.18 mm i.d. 014 µm film thickness) was used as the column. The column temperature was initially increased from 120 °C to 200 °C at a rate of 45 °C/min. Then it was increased to 230 °C at a

rate of 15 °C/minute, and finally to 300 °C at a rate of 30 °C/minute and then kept constant for 3 minutes. For the study, 1 mL of serum was put into a glass tube and 9 mL of type 1 water was added. Solid-phase extraction (SPE) cartridges were lined up in the manifold. Five mL of methanol, 5 mL of methyl-tert-butyl ether (MTBE) and 3 mL of type 1 water were passed through the cartridge, respectively. The serum sample was then loaded into the SPE cartridge. The sample flow rate was set at 6-8 mL/minute. After passing the sample, the cartridge was washed with 3 mL of type 1 water and dried under vacuum for 10-15 minutes. The extract collected at the bottom was discarded and a clean glass tube was placed in the manifold. Collection was done with 5 mL MTBE. After the collected extract was evaporated to dryness under nitrogen at 40 °C bath temperature, 1 mL n-Hexane was added to the tube and mixed by vortex. It was filtered through 0.45 m polytetrafluoroethylene filter and put into a vial and injected into the GC-MS system.

Using the Quechers kit for PCB analysis in urine samples; 5-10 g of the sample was weighed. It was put into a 50 mL Teflon tube. Ten mL of 1% acidified acetonitrile (with acetic acid), containing 100 ng/g Aldrin standard (internal standard) was added to the sample. The mouth of the tube was tightly closed and shaken by hand for about 1 minute. Ready mix containing 6 g magnesium sulphate (MgSO4) and 1.5 g sodium acetate (CH3COONa) was added to the sample. The mouth of the tube was tightly closed and shaken by hand for about 1 minute. It was then mixed by high-speed vortex for 5 minutes. It was centrifuged for 5 minutes at 4,000 rpm. Liquid Extract was transferred to a 10 mL ready-made tube containing 2-8 mL of 400 mg primary secondary amine and 1,200 mg of MgSO4. The mouth of the tube was tightly closed and shaken by hand for about 1 minute. It was then mixed by high-speed vortex for 5 minutes. It was centrifuged at 4,000 rpm for 5 minutes. It was filtered from the upper phase to the vial and delivered to GC ECD/GCMS devices.

The studied PCBs in laboratory tests were as follows: PCB 8, PCB 20, PCB 28, PCB 35, PCB 52, PCB 77, PCB 81, PCB 101, PCB 105, PCB 114, PCB 118, PCB 123, PCB 126, PCB 138, PCB 153, PCB 156, PCB 157, PCB 167, PCB 169 and PCB 189. The qualitative and quantitative results were evaluated. For quantitative measurements, any PCB levels higher than 0.005 mg/kg were noted.

Statistical Analysis

The statistical analyses were performed using SPSS version 16.0. The One-Way ANOVA test was used for comparisons between groups. For subgroup analysis, Mann-Whitney U test and multiple regression analysis were used. A p-value <0.05 was accepted as statistically significant.

Results

In group 1 (n=50), the mean age was 6.7±1.2 years. In group 2 (n=50), the mean age was 5.23±1.25 years. When the anthropometric measurements were compared, the weight SDS in group 1 was 0.72±1.35, the height SDS was 0.77±1.40, the BMI SDS was 0.49±1.09. In group 2, the weight SDS was -0.20±1.47, the height SDS was -0.35±1.54, and the BMI SDS was found to be -0.12±1.28. While there was no difference between group 1 and group 2 in terms of height and BMI SDS, the weight SDS in group 2 were found to be significantly higher than group 1 (p<0.05) (Table I).

When the relationship between the time of birth (preterm or term) and the onset of puberty was evaluated, it was observed that the rate of delivery on time was 88% in group 1 and 84% in the healthy control group. It was observed that the preterm birth rate was 12% in group 1 and 16% in the healthy control group. There was no statistically significant difference in delivery time between children entering early puberty and those in the healthy control group (p>0.05).

Maternal AAM (years) were 12.06±1.25 in group 1 and 12.65±0.92 in group 2 (p=0.006). It was determined that the age of onset of maternal menarche was statistically significantly earlier in group 1 than in group 2 (p<0.05) (Table II).

When the relationship between professions of the

Table I. Anthropometric measurements of the groups

	Study group (n=50)	Control group (n=50)	p-value
Weight SDS	0.72±1.35	-0.20±1.47	**0.008**
Height SDS	0.77±1.40	-0.35±1.54	0.12
BMI SDS	0.49±1.09	-0.12±1.28	0.1

BMI: Body mass index, SDS: Standard deviation score

Table II. The relationship between puberty precocious, premature thelarche and gestational age at birth and maternal menarche age

	Study group (n=50)	Control group (n=50)	p-value
Maternal menarche age	12.06±1.25	12.65±0.92	0.006
Premature born (%)	12	16	
Term born (%)	88	84	0.56

mothers and fathers of both groups and the time of onset of puberty was examined, it was seen that 58% of the mothers in group 1 were housewives, 24% were self-employed and 18% were civil servants, 66% of fathers were self-employed and 34% were civil servants. In group 2, 74% of the mothers were housewives, 14% were self-employed, 12% were civil servants, and 2% of fathers were unemployed, 78% were self-employed and 20% were civil servants. No statistically significant difference was found between family professions and the onset of puberty (p>0.05).

When birth weights were examined, the mean birth weight of group 1 was 3,180 gr ±664 and the mean birth weight of group 2 was 3,048 gr ±641. There was no significant difference between group 1 and group 2 in terms of birth weight (p=0.748).

The distribution of pubic hair growth and breast development stages according to Tanner at the time of admission in the girls were determined such that, in group 1, 28% of patients (n=14) were in pubarche stage 2, 60% of patients (n=30) were in pubarche stage 3, 10% of patients (n=5) were in pubarche stage 4, and 2% of patients (n=1) were in pubarche stage 5. 8% (n=4) were in thelarche stage 2, 64% of patients (n=32) were in thelarche stage 3, 20% of patients (n=10) were in thelarche stage 4, and 8% of patients (n=4) were in thelarche stage 5. At the time of application, delta BA of these patients was determined to be 0 in 22% (n=11) of patients, 1 in 32% (n=16) of patients, 1.5 in 16% (n=89) of patients, 2 in 28% (n=13) of patients, 3 in 2% (n=1) of patients, and 4 in 2% (n=1) of patients.

CPP and Isolated PT Subgroups Results

Twenty-nine out of 50 patients (58%) in Group 1 were diagnosed with isolated PT, and 21 patients (42%) were diagnosed with CPP. Anthropometric measurements were compared, the weight mean SDS in the CPP group was 0.89±1.43, height SDS was 0.88±1.47, and BMI SDS was 0.71±1.05. In isolated PT, weight SDS was -0.49±1.22, height SDS was 0.63±1.31, and BMI SDS was found to be 0.19±1.10. There was no difference between the PP group and PT group. (p>0.05) (Table III).

Maternal AAM (years) were 11.9±1.2 in the PP group and 12.2±1.3 in the PT group (p=0.076). It was determined that maternal AAM was not statistically significantly (p>0.05).

The laboratory tests for differentiating precocious puberty from PT are BA, basal LH, FSH, E2 levels, pelvic ultrasonographic imaging of the ovaries and uterine longest axis and volume dimensions. BA was 1.48±0.83 in the CPP group and 0.85±0.77 in the isolated PT group (p=0.015).

Table III. Anthropometric measurements and laboratory values of CPP and isolated PT patients'

	CPP group (n=21)	Isolated PT group (n=29)	p-value
Weight SDS	0.89±1.43	0.49±1.22	0.29
Height SDS	0.88±1.47	0.63±1.31	0.53
BMI SDS	0.71±1.05	0.19±1.10	0.97
Basal LH (mIU/mL)	1.01±1.38	0.53±0.78	0.10
Basal FSH (mIU/mL)	3.53±1.88	2.42±1.74	**0.016**
Basal E2 (pg/mL)	18.4±14.4	8.76±18.4	**0.00**
Uterine longest axis (mm)	36.9±8.28	29.8±10.4	**0.006**
Right ovarian longest axis (mm)	25.2±8.3	24.2±8.7	0.45
Volume of right ovary (cm^3)	4.18±4.7	4.85±6.9	0.52
Left ovarian longest axis (mm)	24.0±7.1	20.6±6.47	0.14
Volume of left ovary (cm^3)	3.03±3.3	2.47±2.2	0.52
BA	1.48±0.83	0.85±0.77	**0.015**

BA: Bone age, BMI: Body mass index, CPP: Central puberty precocious, E2: Estradiol, FSH: Follicule stimulating hormone, LH: Luteinizing hormone, PT: Prematury telarche, SDS: Standard deviation score

This result is statistically significantly (p<0.05). Uterine longest axis was 36.9±8.28 in the CPP group and 29.8±10.4 in the isolated PT group. Basal FSH (mIU/mL) in the CPP group was 3.53±1.88 and 2.42±1.74 in the isolated PT group (p=0.016). Basal E2 (pg/mL) in the CPP group was 18.4±14.4 and 8.76±18.4 in the isolated PT group (p=0.00). The CPP and the isolated PT subgroups basal FSH, E2 levels, BA and uterine longest axis dimensions results were statistically significantly (Table III).

We were unable to demonstrate any quantifiable levels of PCB remnants in the serum and urine samples of the patients in either group.

Discussion

Our results demonstrated that the patient's location of residence, maternal AAM and their weight had a significant role on PP in those girls aged between 2 and 8 years old. However, we were unable to demonstrate an association between PP and PCBs we studied or any other factors.

As far as we know, in the studies conducted so far, no relationship has been found between PCB exposure and

early puberty in girls. In one study conducted to evaluate intrauterine PCB exposure, they found no relationship between 6 PCB congeners (118, 138, 153, 156, 170, 180) and menarche age and menstrual cycle length in 436 Danish girls at an average age of 19.6. They also demonstrated 14% shorter menstrual cycle times in girls exposed to high doses of 2 PCB congeners in comparison to those exposed to low doses (11). In another study conducted with 192 healthy 9-year-old girls living in New York, Wolff et al. (12) argued that PCB exposure had no effect on breast development and that breast development could be delayed in the group with high PCB exposure and low BMI. In another study, Su et al. (13) reported significantly lower E2 concentrations in eight-year-old children exposed to high levels of Polychlorinated Dibenzo-p-Dioxins and Polychlorinated Dibenzofurans (PCDD/Fs) and PCBs. Moreover, they demonstrated a significant association between PCBs median exposure level and fundus length after adjusting for BA. They concluded that in utero exposure to PCBs resulted in decreased serum E2 concentrations and this was thought to delay the reproductive development of these girls. They also observed a borderline significant effect of exposure level on breast and Tanner stages and found that there was a significant relationship between PCBs median exposure level and fundus length after adjusting for BA (13). Gellert (14) demonstrated that the estrogenic activity of a PCB was associated with decreased neuroendocrine differentiation and premature reproductive aging. Denham (15) showed that prepubertal PCB exposure caused menarche age to occur earlier in girls. In contrast, Vasiliu et al. (16) and Yang et al. (17) showed that PCB exposure in the prenatal and early postnatal period did not affect the age of menarche and pubertal development in girls.

In our study, no PCB residue was found in either group. Therefore, the relationship between PCB exposure and early puberty was not evaluated. The insufficient number of patients can be shown primarily among the reasons for not being able to determine a relationship between precocious puberty and PCB exposure. However, although PCB exposure has an effect on the early onset of puberty, the amount of PCBs may have been reduced to immeasurable levels due to the cross-sectional nature of the study. The individuals in the study group live in and around Izmir. The fact that the industrial establishments in this region have relatively less effect on the formation of PCBs can be considered as another reason why PCBs were not found in the serum samples of the patients. In addition, another limitation of this study is whether the individuals' living spaces were in industrial areas or not. It is thought that meaningful results may be found if they lived in industrial areas which could lead to PCB contamination.

In our study, the weight SDS of the group with early adolescence was found to be significantly higher. However, there was no significant difference between BMI. In the past decades, obesity has become a major health problem in childhood. Obesity can also cause a number of short-term and long-term metabolic disorders including cardiovascular diseases. In addition, it can affect the onset of puberty (18). Several studies have demonstrated that an earlier onset of puberty is associated with obesity in girls. It is known that a certain amount of body fat is a necessity for normal reproductive function. However, increased adipose tissue is a risk factor for pubertal disorders (19,20). Early maturation nearly doubled the odds of being overweight in girls participating in the US National Longitudinal Study of Adolescent Health (21). Slora et al. (22) reported that BMI is significantly associated with the onset of puberty since heavier children reach puberty earlier. Two of the mechanisms suggested to explain the relationship between BMI increase and precocious puberty are high leptin levels and insulin resistance mechanisms. Leptin is a hormone that originates in the adipose tissue and it is essential for normal puberty development. In studies, low leptin levels and delayed puberty were found in girls with less than normal adipose tissue (23). In a study conducted by Matkovic V et al. (24) regarding leptin levels above 12 ng/mL, it was found that every 1 ng/mL increase in leptin level shifts the age of menarche 1 month earlier. However, leptin and insulin levels were not studied in our study.

In the current study, there was an association between PP and maternal AAM and the location of patient's residence. The mean age of maternal menarche was significantly lower in those patients with PP. In concordance, Durand et al. (25) confirmed the high incidence of affected girls with familial early puberty. The mode of inheritance of the phenotype was predominantly maternal. Furthermore, they found that the maternal AAM of the girls with the familial form of CPP was significantly lower than in those with sporadic forms. In addition, we found that those girls living in urban areas carried a significantly higher risk of PP. Similarly, in a study by Ma et al. (26), it was noted that urban Chinese girls were experiencing earlier breast development than the current norm.

Study Limitations

Our study has some limitations. First of all, the size of the study population was low. The second limitation was that it only consisted of patients from a limited area, and therefore did not reflect a wide geographic region. In addition, we could only investigate 20 PBCs. These might explain why we could not detect any of the PCBs in the samples of our patients.

Conclusion

In conclusion, we demonstrated that PCBs we studied do not have an influence on PP in girls aged between 2 and 8 years old. However, living in an urban area, having a higher weight and a lower age of maternal menarche had a positive effect on PP in girls aged between 2 and 8 years old. In order for the endocrine disruptors to show their effects, the time, length and amount of exposure are important. We can conclude that exposure to PCBs in our region is not enough to have any effects on puberty.

Ethics

Ethics Committee Approval: The study was conducted after approval of the Ethics comittee of Ege University Faculty of Medicine (approval date: 29.12.2015; approval no: 15-11/4).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of the participants prior to participation. In addition, written informed consent was obtained from the parents or legal guardians for the publication of this paper.

Peer-review: Externally peer-reviewed.

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Authorship Contributions

Design: Ş.D., Data Collection or Processing: R.B.G.B., S.Ö., Ö.K., Ş.D., Writing: R.B.G.B., R.D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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