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Increased Incidence of Early Onset of Puberty in Girls

Mauro Bozzola[1*], Chiara Montalbano[2], Elena Bozzola[3], Valeria Calcaterra[1,2], Nicola Lazzaro[4], Pietro Ferrara[5], Alberto Villani[3]

[1]Pediatrics and Adolescent Unit, Department of Internal Medicine, University of Pavia, Italy

[2]Pediatric Endocrinology Unit, Foundation IRCCS San Matteo Hospital, Pavia, Italy

[3]Department of Pediatrics, Bambino Gesù Children's Hospital, Italy

[4]Pediatric Unit, S. Giovanni di Dio Hospital, Italy

[5]Institute of Pediatrics, Catholic University, Italy

[*]**Corresponding author:** Mauro Bozzola, Pediatrics and Adolescent Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Via Aselli 43, 27100 Pavia, Italy. Email: mauro.bozzola@unipv.it

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Abstract

Objectives: Early pubertal development has been documented more frequently in recent years, mainly in girls. The reasons for this trend are the subject of intense study.

The aim of our study was to assess the incidence of Precocious Puberty (PP) and Early-Onset Puberty (EP) in girls referred to our Unit, from 2014 to 2016, for early onset of breast development.

Methods: We enrolled 46 girls and collected information about their personal and family history of pubertal development, ethnicity and details of international adoption, as well as any excessive weight gain or obesity in infancy and childhood.

Results: During this 3-year period, we observed no increase in the number of girls with PP (9 cases in 2014, 10 in 2015 and 8 cases in 2016) but an increase in the number of girls with EP was found during the same study period (5 cases in 2014, 4 in 2015, and 10 in 2016).

Conclusions: From our data, we could not establish a clear causative factor. In particular, it is thought that environmental factors, endocrine chemical disruptors, may potentially affect pubertal development in a limited group of subjects, probably in presence of genetic predisposition, when exposure occurs during critical growth periods such as infancy and childhood.

Keywords: Bisphenol; Endocrine disruptors; Phthalate; Puberty; Precocious puberty

Abbreviations: BMI: Body Mass Index; CNS: Central Nervous System: EP: Early-Onset Puberty; EDC: Endocrine-Disrupting Chemicals; FSH: Follicle-Stimulating Hormone; GnRH: Gonadotropin-Releasing Hormone; HPG: Hypothalamo-Pituitary-Gonadal; LH: Luteinizing Hormone; PP: Precocious Puberty; SDS: Standard Deviation Score

Introduction

Puberty results when the Hypothalamo-Pituitary-Gonadal (HPG) axis is activated and the pulsate secretion of the Gonadotropin-Releasing Hormone (GnRH) starts. The onset of puberty is affected by many factors in addition to race; it occurs earlier in girls with early maternal menarche, low birth weight or excessive weight gain or obesity in infancy and early childhood, after international adoption (for unclear reasons, the risk is 10 to 20 times greater for these children), when the biological father is not present in the household, and possibly after exposure to estrogenic endocrine-disrupting chemicals [1-3].

Precocious Puberty (PP) is a rare condition defined by the appearance and progressive development of secondary sexual characteristics at a younger age than in the general population, i.e. for Caucasians, before 8 years of age in girls and before 9 years of age in boys [4]. Precocious puberty is classified as "central"

if it derives from the premature maturation of the HPG axis, or "peripheral" if there is an increase in the production of sex steroids independently of the HPG axis [5]. While in boys, most PP cases reveal an underlying Central Nervous System (CNS) lesion, in girls, the idiopathic form is more frequent than the secondary form.

Early-Onset Puberty (EP) may be observed in girls with the appearance of the breast, which is the first sign of pubertal development, between the ages of 8 and 10 [6]. This condition is self-limiting in most girls but requires careful monitoring as it can progress rapidly, leading to earlier occurrence of the menarche with consequent premature cartilage welding and compromised final stature. In recent years, an increased incidence of PP has been found in many countries such as France [7], Denmark [8] and Korea [9]. Furthermore, since the 1800s a downward trend in the mean age at menarche, from about 16 to 13 years, has been reported, albeit with considerable differences between various countries [1]. Several studies now suggest that this trend has slowed down during the recent years in most industrialized countries, but that it is still ongoing in less developed countries [10-12].

The aim of this study was to assess the prevalence of PP and EP in girls who were referred to our Pediatrics and Adolescent Unit in Pavia, between 2014 and 2016, in whom puberty breast development was evaluated as an initial sign of these conditions.

Patients and Methods

We recorded data for all girls referred to our Pediatrics and Adolescent Unit in Pavia from January 2014 to December 2016 for early onset of breast development. Both the history of the disorder and the physical examination of the girls suggested a progression of pubertal development according to Tanner classification [13]. The girls were all under 10 years of age; girls younger than 8 were diagnosed with PP and those between 8 and 10 with EP.

The clinical and auxological data are shown in Table 1. Height was measured using a Harpender stadiometer. The Body Mass Index (BMI) was calculated according to the formula weight (kg)/height^2 (m^2). Height and BMI were expressed as a Standard Deviation Score (SDS) according to the charts developed by Cacciari, et al. [14]. The bone age was calculated according to the Greulich and Pyle Atlas [15].

	Early-onset Puberty	Precocious Puberty	P value
Chronological age (years)	9.0±0.4	7.5±0.6	**< 0.0001**
Bone age (years)	10.0±1.3	9.6±1.6	NS
Height (cm)	136.5±7.0	130.7±6.5	**0.0049**
Height SDS	0.5±1.2	0.7±1.3	NS
BMI (Kg/m^2)	17.5±2.3	16.9±2.0	NS
BMI SDS	-0.1±1.0	-0.1±0.9	NS
Maternal menarcheal age (years)	11.2±1.5	12.0±1.2	NS
SDS: Standard Deviation Score; BMI: Body Mass Index; NS: Not Significant			

Table 1: Auxological parameters at diagnosis of girls with early start of puberty. Data are expressed as mean ± standard deviation.

At the time of diagnosis, all patients were evaluated through auxological data (with puberty rating), bone age, basal and peak serum levels of gonadotropins after the GnRH stimulation test, serum estradiol values, and both uterine and ovarian measurements by pelvic ultrasound. All the girls underwent magnetic resonance imaging to detect occult intracranial lesions, particularly of the hypothalamic pituitary region. All subjects underwent the GnRH stimulation test (100 μg/m^2 GnRH given i.v. bolus). Serum Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH) (measured at 0, 15, 30 and 90 minutes) and basal estradiol levels were determined by chemiluminescent immunometric assay (Siemens Medical Solutions Diagnostics, Milan, Italy). Pre-pubertal LH levels were < 0.1 IU/l and LH assays had a detection limit of 0.1 IU/l. We considered PP LH levels > 5 IU/l as a diagnostic cut-off.

Thorough pelvic ultrasound examination was used to evaluate uterine length and transverse diameter, fundus/cervix ratio, ovarian volume (calculated using the ellipsoid formula V= D1 x D2 x D3 x 0.5233, where D1 is the largest longitudinal diameter, D2 the largest anteroposterior diameter, and D3 the largest transverse diameter), and the presence of an endometrial echo. Our study considered as pubertal size a uterine length of >= 3.5 cm, a fundus/cervix ratio of >1, an ovarian volume of >= 2 ml, and the presence of an endometrial echo [16].

Children with dysmorphic syndrome, chromosome abnormalities, endocrine or chronic diseases, suspected neurological disorders or CNS pathologies were excluded from the study.

The study was approved by the Ethics Committee of IRCCS San Matteo Hospital of Pavia, Italy, on 17th of May 2016, reference number 20160005680.

Results

In the period from January 2014 to December 2016, we observed 46 girls with early onset of breast development and with both a history of disease and linear growth increase suggestive of progression of pubertal development. Of this group, 27 girls had PP and 19 EP. In both 2014 and 2015, 14 girls were referred to our

unit for early start of puberty, while 18 were referred in 2016.

The EP girls were significantly older and had reached a higher height (Table 1). They also had significantly higher estradiol serum levels at diagnosis (Table 2).

	Early-onset Puberty	Precocious Puberty	P value
Uterine length (cm)	4.2±0.9	3.8±0.7	NS
Uterine diameter (cm)	1.6±0.5	1.9±0.5	NS
Right ovarian volume (cm^3)	2.6±1.6	2.7±2.1	NS
Left ovarian volume (cm^3)	2.3±1.4	2.2±1.6	NS
Serum estradiol (pg/ml)	32.4±12.5	23.2±9.4	**0.0113**
LH peak (mU/ml)	17.8±14.9	18.1±16.5	NS

Table 2: Endocrinological parameters at diagnosis of girls with early start of puberty. Data are expressed as mean ± standard deviation.

Only one of the girls, of Italian origin, had been adopted; 8 girls were non-Caucasian (4 South Americans, 3 Africans and 1 Asian). Of these, 5 were diagnosed with PP (two in 2014 and three in 2016) and 3 girls were diagnosed with EP, all in 2016.

None of the girls were overweight or obese; their BMIs were within the normal range. Furthermore, only one out of the 19 EP girls and 6 out of the 27 PP girls were small for gestational age at birth, suggesting that the early onset of puberty was not due to a low birth weight. Moreover, there was no difference in maternal menarcheal age between the EP and the PP girls (Table 1). Interestingly, during the observation period there was an increase in the number of diagnoses of EP, while the number of PP cases did not change significantly. Specifically, 5 girls were diagnosed with EP in 2014, 4 in 2015, and 10 in 2016 (Figure 1). On the contrary, 9 girls were diagnosed with PP in 2014, compared to 10 in 2015, and 8 in 2016 (Figure 1).

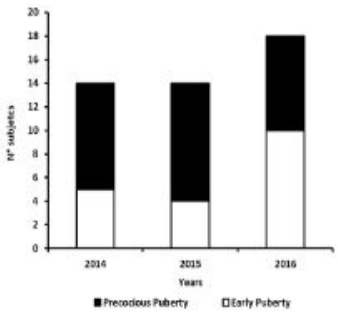

Figure 1: Incidence of early-onset puberty and precocious puberty among 46 girls referred to our Pediatrics and Adolescent Unit in Pavia during 2014, 2015 and 2016.

Discussion

Puberty entails a progressive process starting from childhood and infantile characteristics to full sexual maturity. This process proceeds through the interaction of biological, physical and psychological changes that can accelerate, delay or alter a child's growth process. The onset of puberty results from the interplay between the hypothalamus and pituitary glands, the gonads, the adrenal glands, and peripheral steroid receptor target organs of the reproductive system. Several investigations have suggested that all these physiological interactions can be disrupted by external exposure to agents, which may interact with hormone receptors or interfere with hormone synthesis or metabolism [17-20].

Early onset of puberty may negatively affect the health of adolescent girls. In fact, the decline in the age of puberty onset results in an increased incidence of hormone-related cancers, obesity and diabetes [21]. Our study recorded data from January 2014 to December 2016 from 46 girls referred for early appearance of pubertal signs. During this period, we found an increased incidence of early onset puberty, while that of precocious puberty remained the same. These findings could not be attributed to any improvement in the diagnostic approach, as the clinical and laboratory parameters remained unchanged in our Pediatrics and Adolescent Unit in Pavia during the study period and the diagnoses were always made in accordance with the international guidelines.

Previous studies, however, have shown an increase in the incidence of early or precocious puberty in children who have emigrated or been adopted from undeveloped countries, confirming that profound changes and low socio-economic conditions affect pubertal timing [22]. Among the group of girls in the present study, only one had been adopted while 8 had emigrated from foreign countries with their biological families. Of the latter, 5 patients were diagnosed with PP and 3 with EP; but as all of them had been living in Italy for over three years, their previous change of social and dietary environment was not felt to be relevant to the increased incidence of EP in this study.

Higher prepubertal BMI may affect the rate of pubertal development, leading to earlier appearance of the menarche [23]. In fact, BMI was taken into account in our study since nutrition plays a crucial role as one of the possible reasons for the early onset of puberty. Consuming an adequate, balanced and healthy diet during infancy, childhood and puberty is fundamental for proper pubertal development. Overweight and obese children are far more frequent nowadays, and many studies have demonstrated that excessive eating of high-fat food may trigger the onset of puberty, especially in girls [24]. Nevertheless, in our patients BMI was within normal ranges.

When searching for possible causes of the increased incidence of early onset of puberty in our patients, we considered the possibility that sex estrogen or related environmental factors such as Endocrine-Disrupting Chemicals (EDC) could interfere with the endocrine axis at different levels. The result of this is an increase in the time spam from the initiation of breast development to menarche (about 2 years), indicating a possible estrogen-like effect without concomitant central activation of the hypothalamic-pituitary axis [17].

Moreover, parents generally have a low level of knowledge of the timing of puberty, therefore, children are often referred to the doctor after they have turned eight years of age, at which stage they already present many advanced pubertal signs, implying that the appearance of puberty actually began several months beforehand. We may hypothesize that exposure to EDC, which is ubiquitously present in our food and environment, may play a role in the increased incidence of EP observed in the girls in our study. There are many types of EDCs, most of which have estrogenic and/or anti-androgenic actions and only a few androgenic or anti-estrogenic effects. Thus, it appears plausible that they may interfere with normal pubertal development. It is interesting to note that exposure to environmental factors is similar in all children, due to the increased diffusion of chemical products in food, plastic materials etc., but only a few children experience alterations in puberty timing. It is likely that varying sensitivity to external factors plays a role in pathogenesis; however, it is also conceivable that there are other causative agents or mechanisms, which have not yet been identified.

Conclusions

We found an increase in the occurrence of early puberty in girls referred to our unit during the 3-year study period, while the number of cases with precocious puberty remained constant. It is thought that environmental factors, endocrine chemical disruptors, may potentially affect pubertal development in a limited group of subjects, probably in presence of genetic predisposition, when exposure occurs during critical growth periods such as infancy and childhood. The decline in age of puberty may result in an increased incidence of hormone-related cancers. Therefore, further studies are required in order to understand the causes of the increased occurrence of early puberty in girls.

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Declarations

Ethics approval and consent to participate. All research was carried out in accordance with the Ethical Standards involving human participants. The study was approved by the “Comitato Etico Area di Pavia”, the Ethics Committee of the Foundation IRCCS San Matteo Hospital, on 17th of May 2016, reference number 20160005680. All participants provided parental written informed consent. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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