

Research Paper:

Causes of Precocious Puberty in Children Referred to an Endocrine Clinic in Qazvin City, Iran From 2006 to 2018



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Citation Homaei A, Golmohammadi R, Saffari F. Causes of Precocious Puberty in Children Referred to an Endocrine Clinic in Qazvin City, Iran From 2006 to 2018. Journal of Pediatrics Review. 2021; 9(4):337-346 <http://dx.doi.org/10.32598/jpr.9.4.960.1>

doi <http://dx.doi.org/10.32598/jpr.9.4.960.1>



Article info:

Received: 24 Feb 2021

First Revision: 03 Apr 2021

Accepted: 09 May 2021

Published: 01 October 2021

Key Words:

Precocious puberty, Girls, Boys, Idiopathic

ABSTRACT

Background: Puberty is an essential milestone in a person's life. Studies show that precocious puberty is more common in girls than in boys.

Objectives: The aim of this study was to survey the causes of precocious puberty in children referred to the endocrine clinic in Qazvin city, Iran, from 2006 to 2018.

Methods: This case-series study was performed from March 2006 to June 2018 on patients referred to the endocrine clinic of Qazvin University of Medical Sciences, Qazvin City, Iran, for precocious puberty. To diagnose premature puberty and find its causes, we surveyed sex steroids levels, thyroid function, and, if necessary, performed GnRH test. The patients' height and weight were measured, and their BMIs (Body Mass Index) were calculated. Uterine ultrasound was performed for all girls. Additionally, brain MRI was performed for all boys and girls under age 6 with precocious puberty. X-ray of the left hand was performed to assess skeletal growth acceleration.

Based on the type of puberty, the patients were divided into three groups: Central Precocious Puberty (CPP), Peripheral Precocious Puberty (PPP), and normal variant of puberty. The study data were collected from patients' electronic files and analyzed using SPSS 23.

Results: Out of 724 cases, 642 (88.70%) were girls. The mean age of all children was 7.07 (95%CI: 6.99-7.15) years. About 70.5% of cases had CPP, 5% PPP, and 24.5% normal variant of puberty. Cases of Idiopathic Precocious Puberty (IPP), PPP, Neurogenic Central Precocious Puberty (NCPP), and premature pubarche were significantly higher in girls than boys ($P < 0.001$). None of the boys had NCPP. Most girls had normal BMI, but boys were more obese. Mean bone age and bone age/age ratio were higher in girls with NCPP ($P < 0.001$).

Conclusions: In our study, most girls and boys had idiopathic precocious puberty, and none of the boys had brain lesions. About half of the cases were overweight or obese, indicating the role of obesity in increasing bone age and the onset of puberty.

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1. Introduction

Puberty is an important milestone in a person's life, and researchers regularly monitor changes in the onset of puberty. Familial and genetic factors strongly influence the timing of puberty. However, environmental factors such as nutrition, history of chronic diseases, recurrent infectious diseases, and exposure to chemicals and migration also affect the age of onset of puberty [1]. Along with improved living conditions, changes in food habits, and the environment, the rate of precocious puberty has been increased [2]. The incidence of premature puberty is around 1:5000 to 1:10000, and it is almost ten times more common in girls than in boys [3].

Precocious Puberty (PP) is diagnosed based on the development of breast buds before the age of 8 or menstruation before the age of 9 in girls and testicular enlargement before the age of 9 in boys according to Tanner's diagnostic criteria [4]. Secondary precocious puberty due to early maturation of the hypothalamus-pituitary-gonadal axis is called Central Precocious Puberty (CPP) [5]. CPP without any known causes is called Idiopathic CPP (ICPP). In different studies of the incidence of CPP, girls were ten to twenty times more likely to be affected than boys [6]. CPP in girls can be slowly or rapidly progressive [7]. CPP due to a known central nervous system disorder or an underlying disease is called Neurogenic Central Precocious Puberty (NCPP) [8].

Premature puberty without maturation of the hypothalamic-pituitary-gonadal axis is called Peripheral Precocious Puberty (PPP). PPP can be divided into acquired or congenital. Congenital adrenal hyperplasia is the most common cause of PPP. Whereas, McCune-Albright syndrome and familial testotoxicosis are the rare causes of PPP. Acquired PPP may be due to exposure to endogenous or exogenous sex steroids. Rarely, sex steroid-secreting tumors in the gonads or adrenals, such as ovarian granulosa cell tumors, testicular Leydig cell tumors, germ cell tumors, and adrenocortical tumors or ovarian cysts, may cause PPP. Several sources exist for exposure to estrogen or androgen exogenous, such as oral contraceptive pills, topical estrogen cream, testosterone gel, or anabolic steroids. The premature appearance of pubic hair before the age of 9 in boys and the age of 8 in girls without any other signs of puberty and excluding adrenal disease is considered premature adrenarche [6, 9].

Non-Classical Congenital Adrenal Hyperplasia (NCAH) can be one of the causes of premature adrenarche. NC-

CAH is the most common autosomal recessive endocrine disorder caused by a gene mutation in enzymes involved in adrenal steroid synthesis, leading to a relative deficiency of the enzymes 21-hydroxylase (21-OHD), 11 β -hydroxysteroid dehydrogenase (11 β -HSD), 3- β hydroxysteroid dehydrogenase (3 β -HSD), and StAR mutations. The highest rate of gene mutation is seen in 21-OHD and 11 β -HSD. These patients do not have genital virilization at birth but may present with premature pubarche [9, 10].

Premature thelarche is defined as isolated breast development before 8 in girls. In these girls, bone age matches with chronological age without other signs of puberty. GnRH test was prepubertal in premature thelarche [11]. Vaginal bleeding without any other signs of puberty is considered premature menarche. Premature thelarche, premature adrenarche, and premature menarche are considered a normal variant of puberty or incomplete precocious puberty [12].

In most cases, precocious puberty begins with premature activation of the hypothalamic-pituitary-gonadal axis. Most girls develop idiopathic precocious puberty, while boys are more likely to have a pathological disorder. Precocious puberty is associated with acceleration of growth rate, bone age advancement, and increased levels of sex steroids for age [13]. The size of the uterus and ovaries is more related to bone age than to the chronological age and is correlated with CPP until age 8 [6].

The most serious complication of precocious puberty is short stature in adulthood. These children will be temporarily taller than their age but due to premature closure of the epiphyses eventually become short. In the 2006 cohort in Denmark, the age of onset of puberty in girls was significantly lower than in the 1991 cohort [14]. Recent studies in the United States showed that the age of breast development in American girls begins about 1.5 to 2 years earlier than the age recorded in references [15]. In Korea, the incidence of central Precocious Puberty (PP) was 15.3 and 0.6 per 100000 in girls and boys, respectively. Central PP in girls increased from 3.3 to 50.4 per 100000 girls annually while it increased from 0.3 to 1.2 per 100000 in boys [16]. Most cases of PP in girls older than 6 years are idiopathic, which means no significant lesions in the central nervous system or peripheral hormone secretion; however, boys with precocious puberty are more likely to have a pathological disorder [17].

This study aims to investigate the causes of precocious puberty in children.

2. Materials and Methods

Study participants

This case-series study was performed from March 2006 to June 2018 on patients referred to the endocrine clinic of Qazvin University of Medical Sciences, Qazvin City, Iran. A pediatric endocrinologist examined all patients, and puberty stages were determined based on Tanner diagnostic criteria [4] and recorded in an electronic file; details are fully described below.

Diagnosis of precocious puberty

Precocious puberty was diagnosed based on clinical and paraclinical findings. The presence of two signs of puberty in girls under 8 years of age and boys younger than 9 years with rapid growth and progressive puberty and menarche in girls under 9 years of age was considered premature puberty [18]. Secondary sexual characteristics were determined based on Tanner's diagnostic criteria [4, 19].

The Tanner stages for boys are as follows:

Stage 1: Pre-pubertal;

Stage 2: The scrotum and testicles become enlarged, causing changes in the scrotal skin tissue; Stage 3: Penis growth occurred mainly in terms of length, but with some increase in width along with further growth of the testicles and scrotum;

Stage 4: As the glands develop, the penis becomes longer and broader;

Stage 5: Genitalia size and shape as an adult.

The Tanner stages for girls:

Stage 1: Pre-adolescent;

Stage 2: Breast budding;

Stage 3: Breast and areola enlarged;

Stage 4: The breasts take on a fuller shape with a secondary mound;

Stage 5: Breasts size and shape as an adult.

The pubic hair stages:

Stage 1: Pre-adolescent;

Stage 2: Scanty, long, slightly pigmented hairs at the base of the penis in boys or labia major in girls;

Stage 3: Darker and coarser hair, starting to curl;

Stage 4: As an adult, but not spread to the medial surface of the thigh;

Stage 5: As an adult, spread to the medial surface of the thigh.

Based on clinical examinations and paraclinical findings, patients were divided into three groups according to the type of precocious puberty: CPP (neurogenic or idiopathic), PPP, and normal variant of puberty [13-17].

Also, in terms of paraclinical findings, uterus length of ≥ 35 mm or uterine volume greater than 2.0 mL, [20, 21], peak Luteinizing Hormone (LH) levels of ≥ 5 IU/L after GnRH test, an LH/Follicle-Stimulating Hormone (FSH) ratio of ≥ 2 , and basal ultrasensitive LH > 0.3 IU/L were considered the onset of CPP [12, 20, 22].

Definition of underweight, overweight, obesity, and anthropometric measurements

Patients' height was measured using a wall-mounted stadiometer with an accuracy of 1 mm, and weight by seca scale with an accuracy of 100 g, and BMI is calculated as $\text{weight}/\text{height}^2$ (kg/m^2). We used BMI-for-age tables of the Centers for Disease Control and Prevention (CDC) to diagnose obesity and overweight. $\text{BMI} \leq 5\%$, $5\% \leq \text{BMI} \leq 85\%$, $85\% \leq \text{BMI} \leq 95\%$, $\text{BMI} \geq 95\%$ for age and sex were considered underweight, normal weight, overweight, and obesity, respectively [23].

Blood sample collection, hormonal tests, and imaging

All patients were referred to the same laboratory, and about 5 mL of blood was taken from each.

MRI was performed in boys with central precocious puberty to rule out brain lesions. Electrochemiluminescence (ECL) technology (Cobas 6000, Roche Diagnostics, Indianapolis, IN, the USA) was used for measuring serum levels of Thyroid-Stimulating Hormone (TSH), T4, FSH, and LH and the Enzyme-Linked Immunosorbent Assay (ELISA) technique (Cobas 6000, Roche Diagnostics, Indianapolis, IN, USA) was used for measuring testosterone in those who had testicular enlargement. ELISA technique (Cobas 6000, Roche Diagnostics, Indianapolis, IN, USA) was used for measuring basal FSH and LH, TSH, T4, and estradiol levels and LHRH stimulation test (GnRH: 0.1 mg/m^2) if necessary in girls with breast

development. Pelvic ultrasonography was used to evaluate the uterus and ovaries [6]. Brain MRI was performed in girls younger than 6 with precocious puberty [24]. In patients with premature adrenarche and accelerated growth, we measured 17-hydroxyprogesterone, testosterone, dehydroepiandrosterone sulfate using the ELISA method (Cobas 6000, Roche Diagnostics, Indianapolis, IN, USA), and androstenedione and Adrenocorticotropic Hormone (ACTH) via the ECL method by Elecsys (Germany) tests to diagnose virilizing tumors or NCCAH. The baseline value of 17-OHP was diagnostic between 1.7 and 3.0 ng/mL for NCCAH. After measuring the baseline level of 17-OHP, for the definitive diagnosis of NCCAH, we performed an ACTH test intravenously at a dose of 250 mg/1.73 m², and 17-OHP was measured after 60 minutes. A level of 17-OHP greater than 10 ng/mL was considered NCCAH [15]. X-rays of the left hand and wrist were taken to assess skeletal growth acceleration based on the Greulich and Pyle atlas of skeletal development [25].

Statistical analysis

A complete medical history was taken of all patients, and a careful physical examination was performed. Demographic and anthropometric information, SMR, lab tests, and imaging results were collected from patients' electronic files. The collected data were analyzed by the Chi-square, ANOVA, and independent t test in SPSS 23, and $P < 0.05$ was considered significant.

3. Results

Among the patients referred to the endocrine clinic from 2006 to 2018, 724 children were diagnosed as precocious puberty or normal variant of puberty. The age of the children at the first visit was from 2 to 9 years. Also, 642 were girls (88.70%), and 82 (11.3%) were boys. The mean age of all children was 7.07 (95%CI: 6.99-7.15) years. Besides, 511 cases (70.6%) had central or gonadotropin-dependent precocious puberty, and 36 cases (5%) had peripheral precocious puberty or gonadotropin-independent precocious puberty. Also, 177 (24.5%) of them had a normal variant of puberty. The rates of the premature and normal variant of puberty are presented in Table 1.

Cases of IPP, PPP, NCPP, and premature pubarche were significantly higher in girls than boys ($P < 0.001$). None of the boys had central neurogenic precocious puberty. Six girls with precocious puberty had non-classic Congenital Adrenal Hyperplasia (CAH), and in other cases, no cause was found. The relationship between advanced bone

age and precocious puberty was significant ($P < 0.001$). Also, 52.7% of children with idiopathic precocious puberty and 80% of cases with premature menarche had a BMI $\geq 85\%$. The frequency of premature puberty, parental relationship, age, BW, bone age, and bone age/age ratio are presented in Table 1. The mean age of girls with premature thelarche was lower than the others ($P < 0.001$). Mean bone age and bone age/age ratio were higher in girls with NCPP ($P < 0.001$). About 78.4% of patients with idiopathic CPP and 100% with premature menarche had advanced bone age ($P < 0.001$). The ratio of parental kinship in cases with premature pubarche is higher than in other types of puberty.

The mean \pm SD age of boys and girls were 7.7 \pm 1.5 (range: 2.75-8.92) and 6.9 \pm 0.99 (range: 2-8) years, respectively (Table 2). The various stages of pubarche, breast, and genitalia are shown in Figures 1 and 2. Most patients were presented at stage 2 of puberty. The differences between girls and boys were significant ($P < 0.001$). Table 2 compares BMI, age, weight, height, and birth weight between the two sexes. Most girls had normal BMI, but boys were more obese. The difference between age, height, weight, and advanced bone age in girls and boys was significant ($P < 0.001$). About 58.5% of boys had a BMI $\geq 85\%$, while 49.8% of girls had a normal BMI. Table 3 presents the causes of neurogenic and peripheral PP. Thirty-six children, 7 boys, and 29 girls had peripheral precocious puberty.

A boy with severe hypothyroidism was presented with macroorchidism and suppression of FSH and LH; he was treated with levothyroxine. Six boys with congenital adrenal hyperplasia were developed central precocious puberty before age 9 due to increasing bone age. For this reason, in addition to continuing treatment with glucocorticoids and mineralocorticoids, GnRH agonist was also prescribed for them. Among girls with central neurogenic or organic precocious puberty ($n = 11$), 5 had hydrocephalus and cerebral shunt. Other cases were a 6:6 (year:month) old girl with hypothalamic hamartoma, a 6:6 old girl with a history of glioma from 1 year of age, a cerebral cyst with a history of seizures, a 6:2 old girl with a 5 by 7 mm cyst in the pineal gland, and a case with 4.2 mm cyst in the pituitary gland. A 4.5-year-old girl suffered from premature puberty and cerebral palsy due to brain hemorrhage after falling from a slide in the park.

In girls, the most common cause of premature puberty was hypothyroidism (Hashimoto's thyroiditis). These patients were short, and in most cases, had vaginal bleeding and were in the second stage of breast devel-

Table 1. Relationships of types of puberty with demographic data, bone age, and family proportion in studied children

Variable	No. (%) or Mean±SD						P-Value	
	CPP		PPP (n=36)	Thelarche (n=106)	Pubarche (n=66)	Menarche (n=5)		
	ICPP (n=500)	N CPP (n=11)						
Gender	Male	66(13.2)	0	7(19.4)	0	9(13.6)	0	0.001
	Female	434(86.8)	11(100)	29(80.6)	106(100)	57 (86.4)	5(100)	
BMI	Under weight	15(3.0)	0	1(2.8)	3(2.8)	3(4.5)	0	<0.001
	Normal	217(43.3)	3(20)	16(44.4)	79(74.5)	34(51.5)	1(20)	
	Over weight	115(23.0)	5(50)	11(30.6)	13(12.3)	16(24.2)	1(20)	
	Obese	154(30.7)	3(30)	8(22.2)	11(10.4)	13(19.7)	3(60)	
Advanced bone age		393(78.4)	9(90)	27(75)	36(34)	40(60.6)	5(100)	<0.001
Family proportion		85(17.0)	1(10)	6(16.7)	15(14.2)	18(27.3)	0	0.236
Age (y)		7.2±1.0	6.9±0.7	6.4±1.5	6.5±0.9	6.8±1.1	8.8±0.2	<0.001
Bone age (y)		9.4±1.9	9.9±1.6	9.1±3.0	7.2±1.4	8.2±1.9	12.2 ±1.0	<0.001
Birth Weight (g)		3137±529.3	2880±654	3028.3±586.7	3085.7±463	3168.4±462	3120±164.3	0.438
Bone age/age ratio		1.31±0.24	1.44±0.28	1.46±0.49	1.12±0.19	1.19±0.21	1.38±0.11	<0.001

Abbreviations: BMI, Body Mass Index; CPP, Central Precocious Puberty; ICPP, Idiopathic Central Precocious Puberty; NCPP, Neurogenic Central Precocious Puberty; PPP, Peripheral Precocious Puberty

Variableopment. Four girls had ovarian cysts (4 to 7 cm) with suppressed LH and FSH levels and high estradiol levels. In three girls, administration of exogenous estrogen to treat adhesion of the labia majora led to premature puberty. A 6-year-old girl with stage 3 breast development, ovarian cysts, vaginal bleeding, and bone cysts in the femur bone was diagnosed with McCune Albright syndrome.

4. Discussion

In this study, the most common type of precocious puberty in girls and boys was idiopathic precocious puberty, and IPP was significantly higher in girls than in boys. The prevalence of IPP, premature thelarche, premature pubarche, PPP, and premature menarche in girls was about 68%, 16.5%, 9%, 4.6%, and 0.8%, respectively. Eleven girls (1.7% of girls) had premature central puberty due to brain disorders. The prevalence of IPP in girls was 15 times that of PPP and 39 times that of NCPP.

Most girls (84.5%) were in the age range of 6-7 years, and most boys (81.8%) were 7-8 years old. The prevalence of IPP, pubarche, and PPP in boys was 80.5%, 11%,

and 8.5%, respectively. The most common cause of precocious puberty (86%) in boys was congenital adrenal hyperplasia of type 21 OHD. The secondary onset of CPP may occur in children with PPP with advanced bone age [19]. None of the boys had neurogenic disorders or tumor lesions. Contrary to the findings of other studies, idiopathic precocious puberty in the studied boys was approximately 9.5 times the peripheral precocious puberty; the reason for this discrepancy was unclear.

In a study by Rouhani et al. on 52 patients, 84.6% were girls, and 21 (47.7%) girls had CPP. Three boys (37.5%) had CPP, and three (37.5%) had CAH. About 95% of girls with CPP had idiopathic CPP, and the ratio of ICPP to NCPP was 20:1; whereas 66.6% of boys had neurogenic CPP with an ICPP to NCPP ratio of 1:2. The mean±SDage was 7.43±1.4 years for girls and 5.8±2.1 years for boys. Also, 43.2% of girls (19 of them with premature thelarche) and 25% of boys had normal variant puberty. The female to male ratio in this study was 5.5:1 [8]. The results were similar to our study.

In the Moayeri et al. study, 67.6% of patients were girls, 40% of studied girls had CPP, and 90% had idiopathic

Table 2. Comparison of demographic data and advanced bone age in studied children

Variable	No. (%) or Mean±SD		P-Value	
	Male	Female		
Body Mass Index	Under weight	5(6.1)	17(2.6)	0.008
	Normal	29(35.4)	320(49.8)	
	Over weight	16(19.5)	145(22.6)	
	Obese	32(39.0)	160(24.9)	
Advanced bone age	67(81.7)	443(69.0)	0.020	
Age (y)	7.7±1.5	6.9±0.99	<0.001	
Weight (kg)	37.3±14.4	29.8±8.5	<0.001	
Height (cm)	136.5±16.9	128.0±10.4	<0.001	
Birth Weight (kg)	3222.3±576.2	3110.7±508.9	0.066	

CPP. However, 61% and 39% of boys presented idiopathic CPP and neurogenic CPP, respectively [26]. In Lee et al.'s study on 71 boys, 44 cases (62%) had idiopathic, and 27 (38%) had organic precocious puberty. The mean±SD age at onset of puberty and mean bone age at diagnosis were 7.2±1.5 and 10.2±2.0 years, respectively. Most boys had Tanner stage G2 at the time of diagnosis. In the present study, most boys were in Tanner stage two, and bone age was advanced in most cases (78.6%) with idiopathic precocious puberty [27]. In Shiva et al.'s study on 129 cases referred for premature puberty, 106 (82.2%) were girls. Premature puberty was detected in 43.4% of cases, and 71.4% of them had CPP and 28.6% had PPP. Thirty-nine cases presented with a normal variant of pu-

berty. Their mean±SD age at diagnosis was 6.6±2.5 years for girls and 7±3.9 years for boys. Also, 87.5% of cases with CPP had idiopathic CPP, and girls were more affected than boys. Brain lesions were reported in five cases. Overweight or obesity was observed in 46% of patients with idiopathic PP. Also, 67% of all cases and 53.8% of children with IPP were overweight or obese, while most cases (64.4%) with a normal variant of puberty had normal BMI [28]. In our study, 53.7% of cases with ICPP were overweight or obese. Studies have shown that precocious puberty is directly related to obesity and the age of onset of puberty was lower in girls who were overweight or obese [29-31].

Table 3. Etiology of peripheral and neurogenic precocious puberty in studied children

Variable	No. (%)			P-Value	
	Male	Female	Total		
Etiology peripheral PP	Ovary cyst	0	4(0.6)	4(0.6)	1.0
	Hypothyroidism	1(1.2)	21(3.3)	22(3.0)	0.498
	McCune Albright	0	1(0.2)	1(0.1)	1.0
	Exogenous estrogen	0	3(0.5)	3(0.4)	1.0
	Congenital Adrenal Hyperplasia	6(7.3)	0	6(0.8)	<0.001
Etiology neurogenic PP	Brain mass	0	5(0.8)	5(0.7)	1.0
	Hydrocephaly	0	5(0.8)	5(0.7)	1.0
	Brain Hemorrhage	0	1(0.2)	1(0.1)	1.0

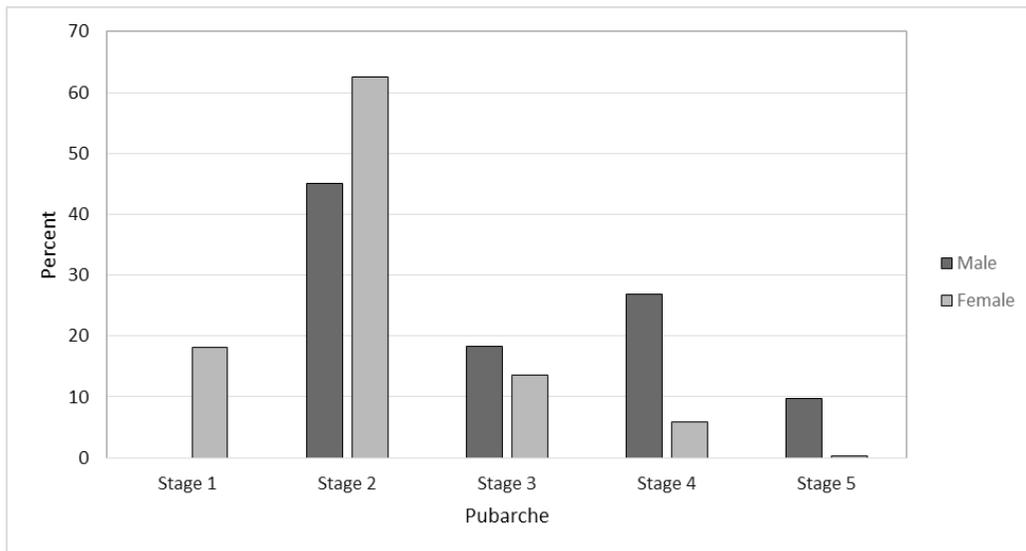


Figure 1. Comparison of various stages of pubarche in two sexes

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Tasnima Ahmed et al., in a study on 71 patients with precocious puberty in Bangladesh, reported more cases in girls (71.8%). The Mean±SD ages of boys and girls were 6.63±1.4 and 4.8±2.1 years, respectively. Also, 43.1%, 9.8%, and 47% of girls had CPP, PPP, and incomplete precocious puberty, respectively. About 35% of boys had CPP, 55% had PPP, and 10% presented with incomplete precocious puberty. Also, 86.3% of girls with CPP had idiopathic CPP, and 83.3% of girls with incomplete precocious puberty had premature thelarche. Hypothalamic hamartoma was the cause of 42.8% of CPP in boys, and 72.7% of boys with PPP had congenital adrenal hyperplasia [32]. In the present study, 63% of girls with a normal variant of puberty had premature thelarche, and none of the boys with CPP had brain lesions.

In Topor et al.'s study in Boston on 50 boys, their mean age was 7.31 years, and 64% were overweight or obese. Most boys (64%) had neurogenic CPP, the most common cause of which was neurofibromatosis type I. In our study, 58.5% of boys were overweight or obese, the average age was 7.7 years, and most boys had idiopathic CPP [33]. In Kim et al.'s study on 226 girls and boys, the chance of girls for CPP was 11.21 times greater than in boys. About 11% of girls had neurogenic CPP. The mean age at diagnosis was 5.25–6.69 years. About 60% of girls with neurogenic CPP were diagnosed after the age of 6 [16]. In the present study, girls were 6.6 times more likely to have idiopathic CPP than boys, and 1.7% of girls had neurogenic CPP.

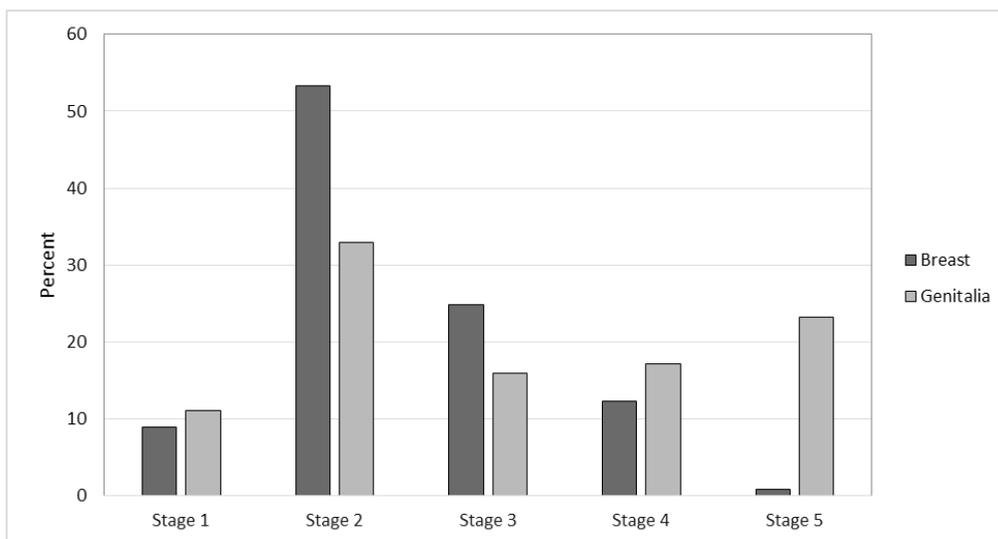


Figure 2. Stages of breast development in girls and genitalia in boys

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In Kiliç et al.'s study, 225 girls with precocious puberty were evaluated, and 56.9%, 24.9%, 18.2%, and 1.6% of them had precocious puberty, premature thelarche, premature pubarche, and pseudo PP, respectively. Bone age in girls with early-onset puberty was more advanced. About half of the patients were 7-8 years old. BMI was significantly higher in girls who had premature puberty. Their mean±SD age at the beginning of puberty was 5.5±1.7 years, and their mean±SD bone age was 6.9±2.5 years. The mean age at onset of premature thelarche was lower than premature pubarche and precocious puberty, that results were similar to our study. Most of our female patients were in the age range of 6-7 years, and BMI was higher in girls with idiopathic CPP [34]. However, in this study, we reported the causes of precocious puberty in children who were referred to our endocrine clinic. Although overweight and obesity can cause premature puberty, due to the declining age of puberty in the country and its importance, it needs further investigation.

5. Conclusion

In our study, the prevalence of precocious puberty was higher in girls than in boys. Most girls and boys had idiopathic precocious puberty, and fortunately, none of the boys had brain lesions. According to the result, it is suggested to conduct studies with larger sample size. About half of the cases were overweight or obese, indicating the role of obesity in increasing bone age and the onset of puberty.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the University of Qazvin (Code: IR.QUMS.REC.1394.166).

Funding

The paper was extracted from the MD thesis of the second author, Department of Pediatrics, Faculty of Medicine, University of Medical Sciences, Qazvin, Iran.

Authors contributions

Conceptualization and supervision: Fatemeh Saffari; Methodology: Fatemeh Saffari; Investigation, writing – original draft, and writing – review & editing: All authors; Data collection: Roghayeh Golmohammadi and Fatemeh Saffari; Data analysis: Ali Homaei.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgements

We would like to thank all the archive personnel of the Clinical Research Development Unit, Qods Hospital, Qazvin University of Medical Sciences, for their cooperation.

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