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ARAŞTIRMA / RESEARCH

Etiological, clinical and biochemical characteristics of 367 children with early pubertal development from the Trakya region of Turkey

Türkiye'nin Trakya bölgesinde erken prepubertal gelişim ile takip edilen 367 çocuğun biyokimyasal klinik ve etiyolojik özellikleri

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Abstract

Purpose: The aim of this study was to describe etiologies, clinical findings, and compare anthropometric properties and biochemical characteristics of children with Precocious Puberty (PP).

Materials and Methods: In this single-center study, 367 patients of whom medical records were reviewed diagnosed as premature thelarche (PT), premature adrenarche (PA), Central PP (CPP), and peripheral PP (PPP). The diagnosis was based on clinical, laboratory, and radiologic investigations and their follow-up.

Results: During six years, 349 girls (%95,1) and 18 boys (%4,9) diagnosed as PP. The most common etiologies were CPP;127 (%34,6), PT;117 (%31,9), PA;112(%30,5) and PPP 11(%3), respectively. CPP group had significantly higher levels of height, weight, body mass index (BMI) and obesity/overweight incidence, estradiol (E2), basal luteinizing hormone (LH), peak LH, and peak LH/ follicle-stimulating hormone (FSH) ratio and higher uterine dimensions compared to the PT group while the PT group had significantly higher levels of peak FSH compared to the CPP group. It is impossible for the laboratory results to exactly match in each case with CPP, and the cases should be evaluated along with other clinical findings.

Conclusion: Our study detected an increase in the frequency of girls referred to with PP signs. However, most

Öz

Amaç: Bu çalışmanın amacı, Erken Puberteli (EP)i çocukların etiyolojilerini, klinik bulgularını tanımlamak ve antropometrik özellikleri ile biyokimyasal özelliklerini karşılaştırmaktır.

Gereç ve Yöntem: Bu tek merkezli çalışmada tıbbi kayıtları incelenen 367 hastaya erken telarş (ET), erken adrenarş (EA), gerçek erken puberte (GEP) ve Periferik Erken Puberte (PEP) tanıları kondu. Tanı klinik, laboratuvar, radyolojik incelemeler ve bunların takibine dayanıyordu.

Bulgular: Altı yıl içinde 349 kız (%95,1) ve 18 erkek (%4,9) EP tanısı aldı. En sık etiyoloji sırasıyla GEP;127 (%34,6), ET;117 (%31,9), EA;112(%30,5) ve PEP 11(%3) idi. GEP grubunda boy, kilo, vücut kitle indeksi (BMI) ve obezite/fazla kilolu insidansı, östradiol (E2), bazal lüteinize edici hormon (LH), pik LH ve pik LH/FSH oranı anlamlı olarak daha yüksekti ve ET grubuna göre uterus boyutları daha yüksekken, ET grubu GEP grubuna göre anlamlı olarak daha yüksek pik FSH seviyelerine sahipti. Her olguda laboratuvar sonuçlarının GEP ile tam olarak eşleşmesi mümkün değildir ve olgular diğer klinik bulgularla birlikte değerlendirilmelidir.

Sonuç: Çalışmamızda EP bulguları ile başvuran kızların sıklığında artış saptadık. EP'li çocukların çoğu, endokrin patoloji insidansı çok düşük olan inkomplet tip olarak

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children with PP were revealed as an incomplete type with a very low incidence of endocrine pathology. The complexity of pathogenesis in PP should lead us to be cautious about the consequences of PP in patients andevaluate their complaints, physical findings, and laboratory work-up seriously, such as a piece of a puzzle.
Keywords:. Central precocious puberty, premature thelarche, premature adrenarche, estradiol, DHEA-

ortaya çıkmıştır. EP' deki patogenez oldukça karmaşıktır ve EP tanılı hasta sonuçları konusunda dikkatli olunmalı ve şikayet, fizik muayene ve laboratuvar bulguları yapbozun bir parçası olarak ciddi bir şekilde değerlendirilmelidir.

Anahtar kelimeler: Gerçek erken puberte, erken telarş, erken adrenarş, östradiol, DHEA-S, FSH,

INTRODUCTION

Early puberty refers to the appearance of secondary sex characteristics before 8 in girls and 9 in boys. The age of onset of puberty can vary depending on different ethnicities, socioeconomic conditions, and environmental factors[1-3].

Early puberty is divided into three variants; central (gonadotropin-dependent, true), peripheral (gonadotropin-independent, pseudo), or benign/non-progressive pubertal variant. Central precocious puberty (CPP) is isosexual and occurs owing to the appearance of secondary sex characteristics with the activation of the hypothalamic-pituitary-gonadal axis. In girls, most CPP cases are idiopathic, whereas, in boys, most CPP cases are associated with organic causes. The most prevalent organic cause known is hypothalamic hamartoma. In peripheral precocious puberty (PPP), secondary sex characteristics are independent of gonadotropin. PPP is gender isosexual or heterosexual[4].

The mechanism underlying the onset of puberty has not yet been clarified. It is known that the leptin secreted from the adipose tissue is the most important stimulant. Studies have reported that puberty has commenced at a younger age in recent years, which is caused by the increase in childhood obesity rates[5]. Moreover, exposure to estrogenic compounds in cosmetic products, drugs (such as insecticides), and disruptive endocrine chemicals can lead to the onset of puberty. Precocious puberty (PP) may lead to decreased target height, early menarche, and behavioural issues, thus requiring an appropriate cure for preventing these issues. An individual's age, height at the onset of puberty, bone age, and puberty staging are essential in treatment decisions[6,7].

Gonadotropin-releasing hormone (GnRH) analogs are used in this treatment owing to the associated benefits of improvement in the predicted adult height, delay in the menarcheal age, and prevention of psychosocial issues caused by puberty[8]. No severe side effects have yet been reported associated with this treatment modality. Furthermore, puberty precocious is associated with a high risk of metabolic syndrome, atherosclerosis, and breast and ovarian cancers at older ages.

Even though several research studies of early puberty have been published, it is not clear whether the incidence of precocious puberty is increasing in some populations[9]. The present study aimed to investigate the demographic, anthropometric and laboratory characteristics of children with early pubertal development, in particular, demonstration of PP types and accompanying factors, mainly obesity and overweight incidence in the Trakya region of Turkey.

MATERIALS AND METHODS

This study was performed at the Department of Pediatric Endocrinology unit, Trakya University Faculty of Medicine. A total of 367 patients who were followed up by the pediatric endocrinology unit for six years with early pubertal development were included in the study. Secondary sex characteristics appeared before the age of 8 in girls and before the age of 9 in boys were included in the study.

The study was approved by the Ethics in Research Committee of Trakya University Faculty of Medicine, Edirne, Turkey (approval number: 2012/16-08). Data including weight, weight SDS, height, height SDS, body mass index (BMI), BMI SDS, target height, target height SDS, bone age, predicted adult height, FSH, LH, estradiol, testosterone, 17-hydroxyprogesterone (17-OH P), androstenedione (AS), dehydroepiandrosterone sulfate (DHEA-S) were retrospectively noted from patients' private clinical files by responsible physicians.

Clinical evaluation

Puberty staging of the cases was performed using the Tanner and Marshall criteria [6] . Turkish children's data were used in weight and height standard deviation score (SDS) measurements. Body mass

index (BMI), BMI SDS, target height, and target height SDS [mother's height SDS+ father's height SDS)/1.61] of the cases were calculated; further, X-rays of the left wrist were obtained, and bone age was determined according to the Greulich and Pyle method. The United Kingdom, cole values were used to calculate BMI SDS [10] . In cases with a bone age of ≥6, the predicted adult height (AH) is according to bone age (BA). BA was calculated according to the Bayley–Pinneau method.

Laboratory evaluation

Cases presented with complaints of thelarche, gonadarche and pubarche required tests were evaluated as below.

Thelarche or gonadarche (testicular growth)

Serum gonadotropins (serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and estradiol (E2) / testosterone (T) levels were checked and 100 mcg i.v. Gonadotropin-releasing hormone (GnRH) stimulation test is performed to identify central precocious puberty (CPP). (0.1 mg/mL ampoule; LHRH Ferring®, Germany); further, LH/FSH levels at 0, 30, and 60 minutes and E2/T levels at 30 min were evaluated.

Pubarche

Serum 17-hydroxyprogesterone (17-OH P), androstenedione (AS), dehydroepiandrosterone sulfate (DHEA-S), testosterone (T) levels were primarily examined, and when necessary—i.e., when basal 17-OHP ≥ 1.5 mg/dL, 250 μg i.v. ACTH (0.25 mg/mL ampoule; Synachten®, France) stimulation test was administered, and serum cortisol and 17-OHP levels at 0 and 60 minutes were measured. Patients with 17-OHP ≥ 10 mg/dL after stimulant were considered to have non-classical congenital adrenal hyperplasia (CAH).

- Cases with CA < 8 years of age and BA = CA, with virilization symptoms (−) and normal serum androgen levels, were diagnosed with PA.
- Cases with CA < 8 years of age and BA > CA, with virilization symptoms (±) and increased serum androgen levels, particularly cases with a 17-OHP level of ≥1.5 ng/mL, were administered the ACTH stimulation test. Cases with peak 17-OHP level of ≥10 ng/mL were diagnosed with non-classical CAH.
- Cases with CA <8 years of age and BA > CA, with virilization symptoms (±) and increased serum androgen, particularly cases with DHEA-S of > 500 μg/dL and a mass detected in adrenal USG were diagnosed with adrenal tumor; cases with increased serum T levels and with asymmetrical testicular symptoms were diagnosed with testicular tumor.

Thelarche

Cases presenting with thelarche were evaluated as follows:

- Cases with chronological age (CA) <2 years of age and BA = CA, with no other symptoms of puberty detected, were diagnosed with PT.
- Cases with CA >2 years of age and BA = CA, with isolated breast development and peak LH response in LHRH test of <5 mIU/mL were diagnosed with PT.
- Cases with CA < 8 years of age and BA > CA, with other symptoms of puberty (±) and peak LH response in the LHRH test of ≥ 5 mIU/mL were diagnosed with CPP.
- Cases with CA < 8 years of age and BA > CA, with other symptoms of puberty (±) and LH and FSH being unresponsive to the LHRH test, were diagnosed with PPP.

Pelvic ultrasonography (USG) was performed, and the length and endometrial thickness of the uterus and, if possible, the size of the ovary were evaluated. A uterine length of >35 mm was considered supportive criteria for early puberty [13].

Gonadarche

- Cases with CA <9 years of age and BA > CA, with other symptoms of puberty (±), symmetrical testicular growth, and peak LH response in the LHRH test of ≥5 mIU/mL were diagnosed with CPP.

The groups were compared among themselves in terms of demographic and anthropometric characteristics and laboratory findings as follows: CPP group (excluding the male cases) vs PT group, CPP group (all cases) vs PPP group, PA group vs CAH group.

Biochemical analysis

5 ml venous blood of each patient was collected, and serum was used to measure basal concentrations of sexual hormones. The Immunochemiluminescence assay (ICMA) method was used in the measurement

of basal LH and FSH levels. DHEA-S levels were evaluated using an electrochemiluminescence assay (ECLIA). 17-OHP and AS measurements were determined using RIA. Serum E2 and total T levels were measured using the chemiluminescent microparticle enzyme (CMIA) method.

Statistical analysis

All data was recorded by two researchers. Descriptive statistics are expressed as mean ± standard deviation or median (minimum-maximum) for discontinuous numeric variables, and categorical variables are expressed as numbers and percentages.

Kolmogorov Smirnov normality test was used to detect the distribution of continuous variables in data analysis. The means of groups were compared using the Mann−Whitney test. For quantitative data, comparisons of three and more groups, ANOVA was used if the data were normally distributed, and the Kruskal−Wallis test was used if the data were not normally distributed. For qualitative data, the chi-square test was used if there were more than three groups, and Fischer's exact test was used if the chi-square test condition was not met. The significance level was selected as $p<0.05$ for all statistical analyses. The SPSS 20.0 statistical program was used.

RESULTS

Out of the 367 cases included in the study, 349 (95.1%) were females, and 18 (4.9%) were males. The female/male ratio was 19/1. According to the diagnostic distribution of the 349 female cases with PP, there were 121 (34.7%) CPP cases, 117 (32.8%) PT cases, 104 (30.5%) PA cases, and 7 (2%) PPP cases, respectively; PPP was the least common. According to the diagnostic distribution of 18 male cases with PP, there were 8 (44.4%) PA cases, 6 (33.3%) CPP cases, and 4 (22.2%) PPP cases, respectively.

When the girls with CPP were etiologically evaluated, 115 (95.1%) cases were classified as idiopathic. In 6 (4.9%) cases, CPP had developed due to organic causes, of which 4 (3.3%) were diagnosed with another disease, syndrome, or tumor (tuberous sclerosis (1), operated astrocytoma (1), head trauma (1), operated meningomyelocele) (1) prior to CPP diagnosis. In addition, hypothalamic hamartoma was detected in two cases (1.6%) during cranial *magnetic resonance imaging (*MRI) performed following the CPP diagnosis.

None of the male cases with CPP diagnosis exhibited organic lesions. In the evaluation of puberty staging of male cases with CPP diagnosis, 6 (100%) cases were observed with pubic hair development stage ≥2, 3 (50%) cases with axillary hair development stage ≥2, 6 (100%) cases with a testicular volume of ≥4 cc.

Six male cases were removed from the CPP group to compare the CPP and PT groups. CA and age of onset of complaints of the cases with PT were significantly younger compared with those of the cases with CPP. Mean weight, weight SDS, height, height SDS, BMI, and BMI SDS values, as well as the incidence of obesity or overweight among the cases with CPP, were significantly higher than those among the cases with PT ($p<0.001$). Tanner's stage 2 breast development was significantly higher in the PT group than in the CPP group, and stage 3 breast development was significantly higher in the CPP group than in the PT group ($p <0.001$). BA, BA/CA ratio and ΔBA−CA were significantly higher in the CPP group than those in the PT group ($p<0.001$). TH, TH SD, AH, and ΔAH−TH were significantly lower in the CPP group than in the PT group (Table 1).

Table 1. Comparison of cases with central precocious puberty and premature thelarche in terms of demographic/anthropometric and laboratory characteristics

Characteristics	CPP (n = 121)	PT (n = 117)	p
	Mean ± SD		
CA (years)	8.3 ± 1.4	3.9 ± 2.8	<0.001*
Age of onset of complaints (years)	7.1 ± 1.0	3.4 ± 2.8	<0.001*
Birth weight (kg)	3.0 ± 0.5	3.2 ± 0.5	0.130
Gestational week	39.2 ± 2	39.2 ± 1.8	0.394
Mother's menarcheal age (years)	12.4 ± 1.5	12.8 ± 1.6	0.053

Weight (kg)			32.2 ± 8.2	16.9 ± 8.9	0.001*
Weight SDS			0.9 ± 1.2	−0.09 ± 1.2	<0.001*
Height (cm)			132.6 ± 10.4	99.5 ± 23.4	<0.001*
Height SDS			0.9 ± 1.1	0.3 ± 1.1	<0.001*
BMI (kg/m²)			18.1 ± 2.7	16.0 ± 2.00	<0.001*
BMI SDS			1.0 ± 1.5	−0.4 ± 1.5	<0.001*
Overweight or obesity, n (%)			62 (51.2)	20 (17.1)	<0.001**
Tanner staging, n (%)					
B_2			62 (51.2)	93 (79.3)	<0.001**
B_3			52 (43)	24 (20.7)	<0.001**
$B_{>3}$			7 (5.8)	-	0.014**
Mean ± SD (n)					
BA (yıl)			9.57 ± 1.8	4 ± 3	<0.001*
BA/CA			1.16 ± 0.1	1 ± 0.1	<0.001*
ΔBA − CA			1.2 ± 1.1	0.1 ± 0.6	<0.001*
TH (cm)			158.3 ± 5 (121)#	160.7 ± 5.0 (110)#	0.001*
TH SDS (n)			−0.4 ± 0.8 (121)#	−0.15 ± 0.8 (110)#	0.006*
AH (cm; n)			156.5 ± 8.7 (120)#	161.4 ± 6.5 (48)#	0.001*
ΔAH − TH (cm)			−1.8 ± 8.9 (120)#	0.7 ± 6.3 (48)#	0.037*
Laboratory results	b FSH (mIU/mL)		3.6 ± 2.0 (121)#	3.2 ± 2.0 (103)#	0.065
	b LH (mIU/mL)		1.4 ± 1.6 (121)#	0.3 ± 0.3 (103)#	<0.001*
	b LH/FSH ratio		0.4 ± 0.5 (121)#	0.1 ± 0.1 (103)#	<0.001*
	E_2 (pg/mL)		30.3 ± 25.3 (121)#	19.2 ± 11.5 (103)#	0.001*
	Post GnRH test	p FSH (mIU/mL)	16.7 ± 11 (88)#	23.5 ± 16.3 (50)#	0.009*
		p LH (mIU/mL)	13.3 ± 12.5 (88)#	4.2 ± 3.0 (50)#	<0.001*
		p LH/FSH	0.9 ± 0.8 (88)#	0.2 ± 0.06 (50)#	<0.001*
	Mean uterine length (mm)		38.5 ± 11.5 (121)#	23.6 ± 8.1 (79)#	<0.001*
	Cases with uterine length ≥ 35 mm, n (%)		82 (67.8)	4 (5.1)	<0.001**

Mann–Whitney U test, *p < 0,05; Pearson chi-square test, **p < 0,05; **CPP:** Central precocious puberty**, PT:** Premature thelarche, **n:** Number of cases, **SD:** Standard deviation, **BMI:** Body mass index, **SDS:** Standard deviation score, **B:** Breast development, **Δ:** Difference, **CA:** Chronological age, **BA:** Bone age, **TH**: Target height, **AH:** Predicted adult height, **b**: Basal**, p**: Peak, **GnRH:** Gonadotropin-releasing hormone, **FSH:** Follicle-stimulating hormone, **LH:** Luteinizing hormone, **E_2:** Estradiol, **#:** Values within parentheses represent the number of cases.

Basal LH, E_2, and b LH/FSH levels were significantly higher in cases with CPP than those with PT (p<0.001), although there was no difference between PT and CPP in terms of b FSH levels. p FSH response to the GnRH test was significantly higher in cases with PT and p LH, and the p LH/FSH ratio was significantly higher in cases with CPP. Compared with the PT group, the mean uterine length in pelvic ultrasonography and the rate of cases with a mean uterine length of≥35 mm were significantly higher in the CPP group (p=0.001; Table 2). GnRH analog treatment was initiated in 67(55.4%) of the female cases with CPP, whereas 54 (44.6%) cases were followed up. All PT cases were monitored.

When the cases with PPP were examined in terms of underlying causes, 6 (54.5%) had CAH (4 females, two males), 3 had McCune-Albright syndrome MAS (females), 1 had a testicular tumor (male), 1 had adrenal tumor diagnosis (male). Out of the female cases with PPP, 4 (57.1%) were heterosexual, and 3 (42.8%) were isosexual PPP, whereas, of the male cases, 4 (100%) were isosexual PPP.

Further, three girls with MAS presented with thelarche. Moreover, 66 (52%) of the cases with CPP was obese or overweight, whereas 4 (36.4%) of the cases with PPP were obese or overweight. There were no differences between CPP and PPP groups regarding BA and BA/CA. TH and TH SDS were low in the CPP group (p< 0.001; Table 3).

When CPP and PPP cases were compared in terms of laboratory results, b FSH and LH levels were higher in cases with CPP (p<0.001). p LH and p FSH responses to the GnRH test were lower in the PPP group (p= 0.001; Table 2).

ACTH stimulation test was performed in 38 cases (32%) presenting with pubic hair development complaints, and 6 cases (5%) with a 17-OHP level of >10 ng/mL were diagnosed with CAH. In the physical examination of the cases with CAH, 4 cases (66.7%) had both pubic and axillary hair development, and 2 cases (33.3%) had only pubic hair development. In addition, cases with CAH were taller compared with those with PA (Table 4).

When PA and CAH were compared in terms of laboratory results, T, 17-OHP, DHEA-S, and AS were significantly higher among cases with CAH. Peak 17-OHP response to ACTH stimulation test in cases with CAH were higher compared with the cases with PA (Table 3). There were no differences between the groups in terms of birth weight, gestational week, and mother's menarcheal age.

Table 2. Comparison of cases with central precocious puberty and peripheral precocious puberty in terms of demographic/anthropometric characteristics and laboratory results

Characteristics	CPP (n = 127)	PPP (n = 11)	P
	Mean ± SD		
Female (Male)	121 (6)	7 (4)	<0.001**
CA (years)	8.3 ± 1.4	6.4 ± 1.8	0.125
Age of onset of complaints (years)	7.1 ± 1	7.3 ± 3.7	0.274
Birth weight (kg)	3.1 ± 0.5	2.9 ± 0.6	0.422
Pregnancy week	39.2 ± 2	38.6 ± 3.7	0.666
Weight SDS	0.9 ± 1.1	0.7 ± 1.6	0.443
Height SDS	0.9 ± 1.1	0.9 ± 1.4	0.601
BMI SDS	1.0 ± 1.3	0.5 ± 1.4	0.189
Being overweight or obese n (%)	66 (52)	4 (36.4)	0.321
Tanner staging n (%)			
B2	62 (51.2)	3 (42.9)	0.555
B3	52 (43)	-	
B>3	7 (5.8)	-	
PH≥2	120 (94.5)	8 (72.7)	0.034**

AxH≥2		64 (50.4)	7 (63.6)	0.0399***
Menarche		18.1 (23)	-	
Mean ± SD				
BA (years)		9.6 ± 1.8	9.5 ± 3.8	0.902
BA/CA		1.1 ± 0.1	1.3 ± 0.4	0.261
TH (cm)		159 ± 5.8	162.3 ± 8.8	0.223
TH SDS		−0.4 ± 0.8	−0.3 ± 0.8	0.347
AH (cm)		157.2 ± 9.2	152.5 ± 7.9 (10)#	0.169
ΔAH–TH		−1.8 ± 8.8 (126)#	−8.1 ± 10.7 (10)#	0.066
Laboratory results	b FSH (mIU/mL)	3.6 ± 2.1	1.2 ± 1.6	0.001*
	b LH (mIU/mL)	1.4 ± 1.6	0.4 ± 0.5	0.003*
	Post GnRH test			
	p FSH (mIU/mL)	16.6 ± 10.9 (94)#	0.9 ± 0.4 (3)#	0.001*
	p LH (mIU/mL)	13.4 ± 12.3 (94)#	0.5 ± 0.2 (3)#	0.001*
	p LH/FSH (mIU/mL)	0.9 ± 0.8 (94)#	0.5 ± 0.02 (3)#	0.545

Mann–Whitney U test, *****p < 0,05; Pearson chi-square test, ******p < 0,05; **CPP:** Central precocious puberty, **PPP:** Peripheral precocious puberty, **n:** Number of cases, **SDS**: Standard deviation score, **BMI:** Body mass index, **AxH:** Axillary hair, **PH:** Pubic hair, **B:** Breast development, **BA:** Bone age, **CA:** Chronological age, **TH**: Target height, **AH:** Predicted adult height, **Δ:** Difference**,** Since one case was <6 years of age, predicted adult height could not be calculated. CPP: Central precocious puberty, PPP: Peripheral precocious puberty, n: Number of cases, SD: Standard deviation, b: Basal, p: Peak, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol, GnRH: Gonadotropin-releasing hormone. #: Values within parentheses represent the number of cases.

Table 3. Comparison of cases with premature adrenarche and congenital adrenal hyperplasia in terms of demographic/anthropometric characteristics and laboratory results

Characteristics	**PA (n=112)**	**CAH (n=6)**	**P**
	Mean ± SD		
Female (Male)	104(8)	4 (2)	0.081
CA	7.0 ± 1.2	7.9 ± 0.9	0.065
Age of onset of complaints	6.4 ± 1.2	6.7 ± 0.6	0.585
Birth weight (kg)	3.1 ± 0.7	3 ± 0.6	0.508
Pregnancy week	39.1± 2.4	39.3±1.6	0.921
Mother's menarcheal age	12.6 ± 1.3	12.8 ± 1.8	0.613
Weight SDS	1.00 ± 1.3	1 ± 1.8	0.946
Height SDS	0.9 ± 1	1.5 ± 1.7	0.528
BMI SDS	0.9 ± 1.6	0.6 ± 1.6	0.557
Being overweight or obese n (%)	57(51)	3 (50)	0.644
Tanner staging n (%)			
PH≥2	109 (97.3)	6 (100)	0.919

$AxH_{\geq 2}$		43 (38.4) (38.4)	3 (66.7)	0.214
Mean ± SD				
BA (yıl)		7.6 ±1.6	10.4 ± 1.9	0.004*
BA/CA ratio		1 ± 0.2	1.3 ± 0.4	0.020*
TA (cm)		161.5 ± 6.0	161.6 ± 8.6	0.990
TA SDS		−0.2 ± 0.8	−0.3 ± 1	0.995
AH(cm)		162 ± 10 (106)#	153 ± 5.7	0.012*
Δ AH-TH (cm)		0.6 ± 8.5 (106)#	−8.7 ± 10.5	0.019*
Laboratory results	T (ng/ml)	0.2 ± 0.3 (63)#	0.5 ± 0.3 (6)#	0.017*
	17OHP (ng/ml)	0.7 ± 0.5 (107)#	6.7 ± 3.5 (6)#	<0.001*
	DHEAS (µg/dl)	81 ± 50 (112)#	139.2 ± 53.4 (6) #	0.007*
	AS (ng/ml)	0.7 ± 0.5 (107)#	2.4 ± 1.8 (6)#	0.045*
	Post ACTH test			
	p 17-OHP (ng/ml)	3.3 ± 1.3 (32)#	29.0 ± 25.0 (6)#	<0.001*

Mann–Whitney U test, *****p < 0.05; **PA:** Premature adrenarche, **CAH:** Congenital adrenal hyperplasia, **SDS:** Standard deviation score; **n:** Count, **PH:** Pubic hair development, **AxH:** Axillary hair development, **CA:** Chronological age, **BMI:** Body mass index, **BA:** Bone age, **TH:** Target height, **AH:** Predicted adult height, **T**: Testosterone, **17-OHP:** 17-hydroxyprogesterone, **DHEA-S**: Dehydroepiandrostenedione sulfate**, AS** Androstenedione, **ACTH:** Adrenocorticotropic hormone, **p:** peak, **#:** Values within parenthesis represent the number of cases.

DISCUSSION

Puberty is a complicated process, and its mechanisms are not fully understood. Most cases of CPP are currently thought to be idiopathic. Moreover, recent studies show that genetic factors play a role in CPP pathophysiology[11].

The incidence of PP is 10–20 times higher among girls than boys, and girls constitute 86%–92% of the cases[12,13]. Our study's female/male ratio was found as 20/1, with 95.1% of the cases being girls.

In one study, among the cases with PP, CPP showed the highest prevalence, followed by PT, PA, and PPP among girls, whereas PA showed the highest prevalence, followed by CPP and PPP among boys. In another study, the prevalence of PA and PT was high, with no cases with PPP[8,9]. In our study, CPP showed the highest prevalence, followed by PT, PA, and PPP among girls, and PA showed the highest prevalence, followed by CPP and PPP among boys.

Cases with breast development above the age of 2 years should be closely monitored because they may rapidly advance to CPP during follow-up. Etiology of PT remains unclear, although it has been suggested that it is caused by increased sensitivity of the breast tissue to estradiol, temporary estradiol secretion from ovarian cysts, and increased estrogen intake with diet[14,15,10,11] The mean age of diagnosis for PT in our study was 3.9 years, which was consistent with those of other studies. Furthermore, Tanner's stage 2 breast development is more common at presentation. Because breast development shows a progressive course, the duration between the transition from one stage to the other of <1.5 years should be considered a risk factor in terms of PP, according to Tanner[16,17]. Similar to other studies, in our study, stage 3 breast development was more common at the presentation in the CPP group compared with the PT group.

When CPP and PT were compared in a study conducted by Vries et al., the age at CPP diagnosis was higher than that in PT as in our study[18]. The proportion of idiopathic CPP reported in various series is 69%–98% among girls and 0%-60% among boys[16-18-20]. In our study, of the total 121 female cases with CPP, 115 (95.1%) cases were idiopathic, whereas

6 (4.9%) cases exhibited CNS pathology[2,13,17,19]. Organic lesions in the CPP etiology are more common among boys; however, our study observed no organic lesions in male cases, attributable to the limited number of cases.

An increase in body adipose mass is suggested as an important factor in the onset of puberty shifting toward earlier ages[6,21]. Increased body weight is one factor that plays a role in the complete activation of the HHG axis[22]. The most important factor is leptin, which is produced by adipose cells and regulates appetite and energy metabolism[23]. In previous studies, obesity and overweight incidence are associated with earlier onset of puberty[24]. In our study, both body weight and BMI SDS of the cases with CPP, along with the incidence of obesity or overweight, were significantly higher compared with cases with PT. In our study, based on the result that body weight is above average in approximately one-fifth of the cases with PT, we state that obesity may be a factor in the etiology of PT development in these children.

Reportedly, in PP, particularly CPP, skeletal maturation and growth rapidly occur at an early age[25]. Therefore, cases with CPP are taller compared with the cases with PT, as in our study. Considering that the height SDS of the cases with CPP is significantly higher, it is possible to state that these results reflect the increased speed in linear growth in CPP[13,18].

Some of the most important characteristics of PT are CA and BA being compatible and the CA/BA ratio being below 1.2. If BA is higher than CA or if BA/CA ratio is >1.2, it is determined whether patients with CPP will have fast progression[16,18]. In our study, similar to other studies, in female cases with CPP, the mean BA of 9.5 years, CA of 8.2 years, BA/CA ratio of 1.1, and ΔBA–CA difference of 1.2 were higher than those in cases with PT. The BA/CA ratio of the cases with CPP was similar to each other and <1.2. Because in puberty, skeletal maturation and BA advancement as an indicator for it are more pronounced in the advanced stages of puberty, the results of our study show that the cases presented within a short period following the emergence of bone symptoms. AH calculated according to the BA of the patients is important in terms of showing whether there will be a loss in the predicted adult height, especially in patients with CPP. Significant losses in AH constitute an indication for treatment[21]. In our study, when cases with PT and CPP were compared, AH was taller in the cases with PT and the height loss in terms of ΔAH–TH was observed in cases with CPP. Therefore, cases with CPP may not be able to achieve their target height, unlike the cases with PT. In our study, target height and target height SDS were significantly lower in cases with CPP than those with PT. Because BA quickly progresses in the case of fast progression of the puberty of these cases with lower TH, the final height may be expected to be short.

Gonadotropin level measurements are important to detect the presence of HHG axis activation and to differentiate between CPP and PT. Increased basal serum LH levels are compatible with increased LH levels following the GnRH stimulation test and are important in diagnosing CPP. A value of 0.3 mIU/mL for basal LH and 12 pg/mL for serum E2 level are accepted as pubertal limits[26]. Basal LH and FSH values were detected to be higher in cases with CPP than those with PT[16,18]. In our study, basal LH, FSH, and E_2 values were higher than those in cases with PT. However, the mean basal E_2 level in the cases with PT in our study was 19.1 pg/mL and above the pubertal level. Although Vries et al. found similar basal E_2 levels in the PT and CPP groups, Partsch et al.[19] found basal E_2 levels at prepubertal levels in half of the cases with CPP. In conclusion, the diagnostic value of E_2 is limited, and an E_2 level of >12 pg/mL is not a sensitive parameter. Thus, the differentiation between PT and CPP cannot be obtained with E_2 levels, but it is a laboratory method that aids the diagnosis. Although LH level is dominant in CPP, FSH level is dominant in PT[19]. A normal basal LH level does not mean the patient is prepubertal, and a pubertal response can be obtained by GnRH stimulation test. In girls, if peak LH and LH/FSH levels are above five mIU/mL and 0.3 mIU/mL, respectively, it is significant for CPP, as shown in our study. Moreover, these values were significantly higher than that in cases with PT[17,19,27,13,15,23]. However, in our study, peak FSH response in cases with PT was significantly higher than in cases with CPP. In our study, similar to other studies, the mean uterine length in cases with CPP was higher than that in cases with PT and was found to be >35 mm. However, there were non-pubertal uterine sizes in cases with CPP and pubertal uterine sizes in cases with PT diagnosis. Based on these results, we state that pelvic ultrasonography results cannot be used alone to distinguish between CPP and PT, but it is a parameter for supporting the diagnosis[1,19,28].

According to the laboratory, clinical and radiological findings at the presentation, GnRH analogue treatment started in 54.3% (69 cases) of the cases with CPP. Treatment indications included completed PP, pubertal LH level after GnRH stimulation, peak LH/FSH ratio at the diagnostic level, abnormal height potential, AH loss during follow-up, and psychosocial and behavioural problems. However, there is no general consensus on this topic.

So far, mutations in KISS1, KISS1R, MKRN3, and DLK1 have been described as variants leading to CPP, with mutations in MKRN3, which identified as the most common genetic etiology[29]. Specific genes contribute to the variety of pubertal timing by demonstrating which genetic loci are more significiant[30].

The prevalence of PPP was 3% in our study, and as in literature, the least prevalent type of puberty was PPP, which is more common in girls than in boys[10].

In our study, 54.5% (n=6) of the cases had CAH, 27.3% (n=3) MAS, 1 case had a testicular tumor, 1 case had adrenal tumor diagnoses, and the number of cases with isosexual PPP was higher than the number of heterosexual PPP. Therefore, PPP findings may be a clinical reflection of much more severe pathology, and thus, especially testicular, adrenal, and ovarian tumors must be considered. In compliance with the studies, we also found the weight and BMI SDS of the CPP and PPP cases to be similar[12,16]. This mechanism may be explained by adrenal steroidogenesis in cases with CAH and adrenal tumor and increased estrogen in cases with MAS[11].

In PPP, FSH and LH levels are suppressed. FSH and LH levels do not increase with the GnRH stimulation test either. E_2 in girls and T in boys are at pubertal levels and can be found too high according to the etiology[31]. In our study, peak LH and FSH levels with the GnRH stimulation test were lower among cases with PPP than CPP. Basal LH and FSH levels were increased in cases with CPP but suppressed in cases with PPP.

The average age of onset for PA in our study was 6.39 years. PA generally occurs between the ages of 3–8, but there have also been cases with an onset at 6 months[31,32]. A large majority of our cases presented with the complaint of pubic hair development, but similar to literature, there are also cases with axillary hair development as the initial complaint[31]. Increased adrenal steroid levels were more pronounced for CAH compared to PA. Depending on the increase in DHEA-S, a progression is observed in the bone age in both disease groups[33,34]. Therefore, late diagnosis in cases with CAH may cause more advanced bone age and, thus, a decrease in height gain.

Since PA occurs secondary to the early development of the adrenal gland, adrenal androgens such as DHEA, DHEA-S, androstenedione, and testosterone levels are increased. The sensitivity and selectivity of basal 17-OHP levels above 2 ng/mL are very high in CAH, and in these cases should be administered an ACTH stimulation test. Similarly, in our study, basal 17-OHP, DHEA-S, AS, and T levels were higher than 17-OHP response to the ACTH stimulation test in both CAH and PA groups, while they were higher in cases with CAH[31]. If CAH is not diagnosed during the early period, it leads to advanced BA, short stature, and decreased fertility during the adult period. A differential diagnosis of PA cases must be performed with a physical examination and bone age for non-classical CAH[34].

Ongoing research on these patients is needed. The impact of early puberty on reproductive physiology, long-term outcomes, obesity, metabolic syndrome, adult height, psychological aspects and investigation of comparative effectiveness of different therapies might be the next step to clarifying disease pathogenesis in a straightforward way.

The limitation of this study is that statistical power analysis could not be done. Medical records of patients who were followed up by a pediatric endocrinology clinic with complaints of precocious puberty were retrospectively evaluated.

In conclusion, PP is mainly a problem in female children, and a large portion of the cases consists of CPP and PT. Therefore, performing a cranial MRI to detect organic pathologies caused by CPP is extremely important. It is necessary to take a detailed history, perform physical examination and conduct laboratory tests in cases with PP. Therefore, informing and training parents and primary care physicians regarding early puberty is essential to ensure early diagnosis and treatment of the cases. In addition, suspected cases with PP must be referred to a pediatric endocrinology specialist for the correct diagnosis and therapeutic approach.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SK, FT, NS; Veri toplama: DB, SK, FT; Veri analizi ve yorumlama: NS, SK, FT; Yazı taslağı: SK, FT; İçeriğin eleştirel incelenmesi: SK, FT, DB; Son onay ve sorumluluk: SK, DB, NS, ED, FT; Teknik ve malzeme desteği: -; Süpervizyon: SK, FT; Fon sağlama (mevcut ise): yok.

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