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Evaluation of Clinical, Laboratory and Radiological Findings in the Differential Diagnosis of Premature Telarche and Central Puberty Precocious

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ABSTRACT

Objective: Central puberty precocious (CPP) is defined as the development of secondary sex characters due to the activation of the hypothalamus-pituitary-gonadal axis before the age of eight in girls. Premature telarche (PT) is defined as isolated breast development in girls without other findings of puberty. We aimed to evaluate the clinical, laboratory and radiological findings used in the differential diagnosis of PT and CPP.

Methods: The study included girls who applied to our pediatric endocrinology outpatient clinic between December 2015 and December 2019 with the complaint of breast enlargement that started before the age of 8 years and were diagnosed with SPP or PT. Retrospectively, patients' calendar age, bone age, bone age/calendar age ratio, anthropometric variables, puberty stages, luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol levels, ovarian and uterine volumes were examined.

Results: The study included sixty-five girls 53.8% PT (n=35) and 46.2% CPP (n=30). Height standard deviation (SD) values (p=0.008), basal LH, FSH and estrodiol levels (p=0.029, p=0.008, p=0.011, respectively), right and left ovaries and uterine volumes (p=0.030, p=0.008, p=0.039 respectively) bone age (p=0.039), and bone age/calendar age ratios (p=0.024) were found different between two groups. The importance order of the parameters used in the differential diagnosis of CPP and PT was found as basal LH level, ovarian volume, height SD value, and estrodiol level.

Conclusion: In our study, ıt was determined that our patients with CPP were taller than their peers with PT, had higher LH, FSH and estrodiol levels, larger ovarian and uterine volumes, higher bone ages and higher bone age/calendar age, and the most important parameter in diagnosis was basal LH level.

Keywords: Precocious puberty, breast, puberty, girls, secondary sex characters, differential diagnosis

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INTRODUCTION

Puberty is a transitional period accompanied by the development of secondary sex characteristics and psychosocial maturation. Precocious puberty (PP) is a clinical condition characterized by the early development of secondary sex characters compared to the population average. Early puberty can be classified as central precocious puberty (CPP), peripheral PP, and variants of normal puberty (1,2). CPP is defined as the development of secondary sex characteristics due to the activation of the hypothalamus-pituitary-gonadal (HPG) axis before the age of eight in girls and nine in boys (3-5).

Premature thelarche (PT) is isolated breast development before the age of eight without other clinical signs of puberty. PT is considered a variant of normal puberty, is not considered pathological, and is usually self-limiting, does not cause acceleration in skeletal development and shortens the time to completion of puberty. PP, on the other hand, results in early and rapid skeletal development and premature closure of the epiphyses, leading to a shorter final height of children compared to their genetic potential. In addition, 13% of PT cases may progress to PP (4). Distinguishing these two conditions is important for early diagnosis and treatment of PP (6). In our study, it was aimed to evaluate the clinical, laboratory and radiological findings used in the differential diagnosis of PT and CPP.

METHODS

The study included girls who applied to the pediatric endocrinology outpatient clinic of our hospital between December 2015 and December 2019 with the complaint of breast enlargement that started before the age of 8 and were diagnosed with CPP or PT (age matched with the group diagnosed with CPP). Retrospectively, patients' calendar age (years), bone age (years), bone age/calendar age ratio, anthropometric variables [body weight, height, body mass index (BMI) and standard deviation scores (SDS)], pubertal stages, luteinizing hormone (LH) level, follicle stimulating hormone (FSH) level and estradiol (E_2) level, and ovarian and uterine volumes evaluated by pelvic ultrasonography (USG) were examined.

Anthropometric measurements were made with the child's shoes and top clothes removed and in the morning on an empty stomach. Body weight was recorded as "kg" and height as "cm" by measuring with a stadiometer. Body weight and height SDS values were calculated (7). BMI; SDS values were calculated by calculating BMI= body weight (kg)/height $(m)^2$ formula (8). All patients were examined by the same pediatric endocrinologist and their pubertal stage was determined, pubertal staging was performed according to the Marshall and Tanner method (9). Bone age was evaluated according to the Greulich-Pyle method (10).

Uterine length, endometrium thickness, and three-dimensional measurements of the ovary from the suprapubic USG were recorded retrospectively. Uterine and ovarian volumes were calculated according to the longitudinal ellipsoid model with the formula (cm) x transverse diameter (cm) x 0.5236.

Among the girls who applied with breast development that started before the age of 8; cases with pubertal response to the LH-releasing hormone (RH) stimulation test applied to patients with advanced somatic development and advanced bone age (bone age more than 2 SDS according to the chronological age) were considered SPP (peak LH ≥5 mIU/mL). Cases that did not meet these criteria were considered PT. Cases who were initially diagnosed with PT and met the CPP criteria at follow-up were not included in the study. In addition, cases with missing data, peripheral, and CPP cases with organic pathology detected by cranial/pituitary magnetic resonance imaging were not included in the study. The data of patients diagnosed with CPP and PT were compared.

The study was carried out in accordance with the Declaration of Helsinki Principles and approval was obtained from the Ethics Committee of Hitit University Faculty of Medicine (decision no:194, date: 11.03.2020).

Statistical Analysis

Statistical analyzes in our study were performed using the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normality distribution of the retrospective data was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean ± SD in normally distributed data, median (minimum-maximum) in non-normally distributed data, and categorical data as numbers and percentages (%). Student's t-test, Mann-Whitney U test were used to compare groups, and Fisher's Exact chi-square test was used to compare group ratios. It was considered statistically significant when the p value was <0.05. Binary logistic regression analysis was used with the enter method to determine the factors that are effective in the differential diagnosis of CPP and PT.

RESULTS

Sixty-five female patients, 53.8% (n=35) of whom were diagnosed with PT and 46.2% (n=30) with CPP were included in the study. The mean age of the cases was 7.00±0.61 years (5.91-7.90) in patients with PT and 7.19±0.76 years (5.10-7.91) in patients with CPP. There was no statistical difference between them (p=0.285).

While all of the patients diagnosed with PT (n=35) applied with the complaint of breast enlargement, 73.3% of the patients diagnosed with CPP (n=22) had breast enlargement, 16.7% (n=5) had pubic hair growth, and 6.7% (n=2) had pubic and axillary hair growth, 3.3% (n=1) had breast enlargement and pubic hair growth. There was no statistical difference between the two groups in terms of application complaints difference was detected (p=0.001).

The median (median) puberty stage was 2 (2-3) in both groups, and pubic or axillary hair growth was not detected in any of the cases diagnosed with PT. On the other hand, 36.6% (n=11) of the patients with CPP had pubic hair and 26.6% (n=8) had axillary hair. There was no statistical difference between the two groups in terms of puberty stage (p=0.385). The anthropometric features

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of the cases are shown in Table 1, and their laboratory and radiological features are shown in Table 2.

Basal LH level, ovarian volume, height SD value and estradiol level among the parameters used in the differential diagnosis of CPP and PT; Considering the Hosmer and Lemeshow test, it was found to be suitable for logistic regression and statistically significant ($p<0.05$) (Table 3).

DISCUSSION

In our study, our patients with CPP were taller than their peers with PT, had higher LH, FSH and estradiol levels, larger ovarian and uterine volumes, had more advanced bone ages and had higher bone age/calendar age ratios, and the differential diagnosis was the most common and we determined that the most important parameter is the basal LH level. Early recognition of gonadal axis activation will enable early recognition of CPP and PT cases and timely initiation of treatment to ensure adequate height gain in cases with CPP.

Anthropometric measurements are important variables in differentiating central puberty precocious and PT cases. Progression in bone age, increase in growth rate and body weight are expected findings because of sex hormones in CPP cases (11). Kılıç et al. (12) found significantly higher height, weight, and BMI-SD values in CPP cases compared to the PT group. In the study of Çatlı et al. (13), BMI-SD value was found to be twice as high in the CPP group as in the PT group, but the difference was not statistically significant. Similarly, in our study, the BMI-SD value was found to be higher in the group with CPP compared to the group with PT, but no statistical difference was found. In the study of Vurallı et al. (14), patients with CPP had higher bone age, height and BMI SDS at diagnosis than patients with PT. In our study, in accordance with the literature, the height SD value was found to be significantly higher in girls with CPP than in girls with PT. These findings show that anthropometric variables, especially the height SD value, are important clinical findings that support and distinguish the diagnosis when evaluating CPP and PT cases.

Table 1. Anthropometric features of cases diagnosed as premature thelarche and central puberty precox

	Premature telarch (n=35) ($\bar{x}$±SD) (minimum-maximum)	Central pubertal precox (n=30) ($\bar{x}$±SD) (minimum-maximum)	p-value
Age (years)	7.00±0.61 (5.91-7.90)	7.19±0.76 (5.10-7.91)	0.277[1]
Body weight SDS	1.05±0.91 (-1.15-2.53)	1.11±1.07 (-0.87-3.46)	0.821[2]
Height SDS	0.36±0.93 (-1.63-2.11)	1.11±1.26 (-1.32-3.35)	0.008[2]
BMI SDS	0.75±0.87 (-0.92-2.69)	1.11±0.74 (-0.36-2.20)	0.084[2]

[1]Mann-Whitney U test, [2]independent t-test, SD: standard deviation, SDS: standard deviation score, BMI: body mass index, $\bar{x}$: average

Table 2. Laboratory and radiological characteristics of cases diagnosed with premature telarche and central pubertal precox

	Premature telarch (n=35) ($\bar{x}$±SD) (minimum-maximum)	Central pubertal precox (n=30) ($\bar{x}$±SD) (minimum-maximum)	p-value
LH (mIU/mL)	0.36±0.17 (0-0.68)	0.86±1.72 (0.1-9.41)	0.029[1]
FSH (mIU/mL)	2.07±1.46 (0-6.47)	3.2±1.95 (0.2-7.79)	0.008[1]
E_2 (pg/mL)	7.8±3.1 (5-11)	14.8±15.3 (5-60)	0.011[1]
Right ovarian volume (mm^3)	1,204±856 (243-3944)	1,864±1,388 (187-5,040)	0.038[2]
Left ovarian volume (mm^3)	1,198±907 (227-3808)	2,314±2,055 (178-9,090)	0.013[1]
Uterine volume (mm^3)	1,519±882 (346-4,257)	2,585±2,786 (144-12,402)	0.039[1]
Bone age	7.6±0.95 (5-8.83)	8.45±1.04 (5.75-11)	0.003[1]
Bone age/calendar age ratio	1.09±0.12 (0.8-1.4)	1.18±0.16 (0.96-1.3)	0,024[1]

[1]Mann-Whitney U test, [2]independent t-test, SD: standard deviation, $\bar{x}$: average, LH: luteinizing hormone, FSH: follicle stimulating hormone

Today, various hormonal methods such as measurement of basal and stimulated gonadotropin levels are used in the diagnosis of CPP, in addition to clinical findings such as growth rate and advanced bone age. However, there is no diagnostic method that can definitively distinguish CPP from PT (14). Neely et al. (15) evaluated 49 female patients with CPP and found that the diagnostic value of gonadotropin-releasing hormone (GnRH)-stimulated FSH level was low, whereas the basal LH level measured by the third-generation measurement method (ICMA) was more reliable. In the same study, a strong positive correlation was shown between GnRH-evoked LH and basal LH levels (15). In addition, many studies have suggested that baseline LH level can be used in the differential diagnosis of CPP and PT (16-18). In studies evaluating PT and CPP cases in the literature, the baseline LH value was found to be higher in CPP cases than in PT cases (16). Çatlı et al. (13) also found findings supporting this in their study. In a study conducted in our country, in which 344 cases were included, the basal LH level was found to be significantly higher in patients with CPP compared to the group with PT (14). Consistent with the literature, in our study, the basal LH levels of our subjects with CPP were found to be higher than their peers with PT, and the most important parameter used in the differential diagnosis of CPP and PT was the basal LH level. This result supports the knowledge that the basal LH level can be used as a screening test in the diagnosis of CPP.

USG is frequently used for internal genital imaging of girls because of its well-known advantages such as being inexpensive,

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Table 3. Logistic regression analysis of parameters used in the differential diagnosis of central pubertal precox and premature telarche

	Univariate logistic regression						Hosmer and Lemeshow test	
	B	SE	p-value	OR	%95 OR		Chi-square value	p-value
					The lower limit	Upper limit		
Basal LH level	4.158	1.459	0.004	63.9	3.661	1116.728	13.408	0.900
Ovarian volume	1.555	0.719	0.009	4.9	1.856	12.812	9.984	0.712
Height SD value	1.451	0.497	0.013	4.3	1.610	11.314	9.557	0.215
Estrodiol levels	0.181	0.083	0.029	1.2	1.018	1.411	5.188	0.520

S.E: standard error, OR: odds ratio, SD: standard deviation, LH: luteinizing hormone

easily accessible, fast, reliable, reproducible, and noninvasive, and not causing radiation exposure (19,20). The size of the uterus and ovaries, fundo-cervical ratio and endometrial thickness provide detailed information about the size and distribution of ovarian follicles (20). The transformation of the uterus from tubular to bulbous, enlargement in its volume, increase in the corpus/cervix ratio, and the thickening of the endometrium are the symptoms indicating estrogen exposure (21). Haber et al. (22) reported that measurements of uterus and ovarian sizes were useful in distinguishing patients with SPP from patients with PT. In the study of Battaglia et al. (21), it was stated that uterine length and ovarian volumes were increased in patients with SPP. Similarly, in our study, our cases with SPP were found to have larger ovarian and uterine volumes than their peers with PT. In the study of Vurallı et al. (14), although they detected increased uterus and ovarian size on pelvic USG in accordance with advanced pubertal stage in patients with SPP, none of these factors were found to be significant as criteria to be used in the differential diagnosis of SPP and PT in multivariate logistic regression analysis found (14). Della Manna et al. (23) found that bone age was advanced, height and growth rate as well as uterus and ovarian volumes were increased in patients with CPP. In this study, like the study of Vurallı et al. (14), growth rate-SD value was found to be the only important anthropometric finding to be used to differentiate patients with CPP and PT in multivariate regression analyzes. When the order of importance of the parameters used in the differential diagnosis of CPP and PT in our study was determined by logistic regression analysis, the order of importance was determined as basal LH level, ovarian volume, height SD value and serum estradiol level. In conclusion, although various clinical findings can be used in the differential diagnosis of CPP and PT, it is difficult to detect hypothalamic-pituitary-pituitary axis activation based on clinical findings alone (14). The results of our study show that laboratory findings are supportive variables for clinical findings, and the differential diagnosis of CPP and PT should be made by evaluating laboratory and clinical findings together.

Study Limitations

The most important limiting factor of our study is that it was conducted retrospectively. Patients whose data could not be accessed due to insufficient enrollment had to be excluded from the study, and as a result, a limited number of patients could be included in the study.

CONCLUSION

In conclusion, basal LH level is the most important parameter that can be used in demonstrating HPG axis activation and in the diagnosis of SPP in girls presenting with early breast development. Clinical findings such as anthropometric measurements, ovarian and uterine volumes determined by pelvic USG, advanced bone age and increased bone age/calendar age ratio are supportive data that can be used in the differential diagnosis of SPP and PT in addition to laboratory findings. However, it should not be forgotten that laboratory findings are supportive variables and should be evaluated together with clinical findings.

Ethics Committee Approval: The study was carried out in accordance with the Declaration of Helsinki Principles and approval was obtained from the Ethics Committee of Hitit University Faculty of Medicine (decision no: 194, date: 11.03.2020).

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