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Original Research

Comparative Analysis of Girls With Slowly Progressive Central Precocious Puberty Vs. Rapidly Progressive Central Precocious Puberty: Single-Center Experience

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Abstract

Objectives: Central precocious puberty (CPP) can present as either slowly progressing CPP (SP-CPP) or rapidly progressing CPP (RP-CPP). The speed of progression is critical in determining treatment decisions. This study aims to compare the clinical data between patients who received treatment and those who did not, and to identify factors that may influence the progression in cases of RP-CPP.

Methods: This single-center retrospective observational study includes 406 female patients aged 5-8 years who were followed for CPP at the pediatric endocrinology clinic between 2021 and 2023. The patients were categorized into two groups: those with SP-CPP who did not receive gonadotropin-releasing hormone agonist (GnRHa) treatment (n=252) and those with RP-CPP who did receive GnRHa treatment (n=154). Patients were analyzed according to clinical, laboratory, and radiological findings.

Results: The median age at onset of pubertal signs were 7.2 years (Range 5-8) for the SP-CPP group and 7 (5-8) years for the RP-CPP group (p=0.352). In univariate analysis, Tanner breast stage, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, peak LH levels, and bone age/chronological age ratios were significantly higher in the RP-CPP group. In multivariate logistic regression analysis, Tanner breast stage (p=0.001) and the bone age/chronological age ratio (p<0.001) were found to be a significant parameter, while other variables were not significant (p>0.05).

Conclusion: In this cohort, the bone age/chronological age ratio is a significant parameter for early detection of rapidly progressing precocious puberty cases. It is crucial to classify early puberty cases by evaluating clinical, laboratory, and radiological findings collectively and to make treatment decisions based on individual assessments.

Keywords: Bone age, chronological age, GnRHa treatment, precocious puberty

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Central precocious puberty (CPP) is characterized by the early activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in the early onset of pubertal signs in children. This condition is defined by the onset of pubertal development before age 8 in girls and before age 9 in boys.[1, 2] Central precocious puberty can be classified based on the clinical course, progression of puberty, and growth rate into slowly progressing CPP (SP-CPP) and rapidly progressing precocious puberty (RP-CPP). In SP-CPP, pubertal signs and hormone levels increase gradually, whereas RP-CPP may exhibit an aggressive course, where monitoring alone is insufficient and early diagnosis and treatment are crucial for preserving final height.[2, 3]

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This study aims to: (1) examine the anthropometric measurements and hormonal values of girls aged 5-8 years presenting with pubertal signs; (2) compare the presenting features, anthropometric, and pubertal findings of treated and untreated patient groups; and (3) highlight the importance of these data in making treatment decisions.

Methods

A total of 406 girls diagnosed with CPP and followed up in the pediatric endocrinology unit between 2021-2023 were included in this single-center, retrospective observational study.

Girls with a starting age of pubertal signs ≤8 years and those who started idiopathic puberty without menarche were included. Cases of peripheral precocious puberty, patients with organic lesions detected on cranial magnetic resonance imaging, secondary precocious puberty caused by cerebral palsy or hydrocephalus, accompanying systemic diseases, history of medications potentially affecting the HPG axis, growth hormone deficiency, uncontrolled thyroid disease, or adrenal-gonadal pathology, any metabolic or genetic diseases that causes CPP were excluded from the study.

The patients were divided into two groups by evaluating their clinical findings during a minimum 6-month follow-up period: RP-CPP group, also receiving gonadotropin releasing hormone agonist (GnRHa) treatment (n=154), and the SP-CPP group, not receiving GnRHa treatment (n=252). The criteria for CPP included the onset of secondary sexual characteristics before age 8, increased double wall thickness of the endometrium, a uterus long axis >35 mm on pelvic ultrasonography (USG), a basal Luteinizing Hormone (LH) value>0.2 mIU/L, and bone age (BA) equal to or greater than chronological age (CA). Inclusion criteria for the RP-CPP group included breast development progressing through stages within 6 months, rapidly advancing BA and growth rate exceeding that of healthy children. Patients not meeting these criteria were classified as SP-CPP.[3]

Patient Data and Anthropometric Measurements

Patient anamnesis, the duration of pubertal signs, and pubertal stages according to Tanner classification were obtained from electronic system records. Birth weight, gestational age, and identification of patients born small for gestational age (SGA) were noted. Patients born before 37 weeks of gestation were considered preterm. Birth weight was expressed as a standard deviation score (SDS) according to gestational age. Children with a birth weight SDS below 2 were classified as SGA.

For anthropometric measurements, a calibrated wall-mounted Harpenden Stadiometer (Holtain Ltd, Crymych, UK) was used. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square meters. All measurements were expressed as SDS according to national standards. Patients were categorized based on BMI SDS according to World Health Organization criteria. Thus, those with BMI SDS between 1.3 and 1.8 SDS were considered overweight, and those with BMI SDS ≥1.8 SDS were considered obese.[4]

Laboratory Examinations and Radiological Imaging

Luteinizing hormone, follicle-stimulating hormone (FSH), and estradiol (E2) levels of all cases were evaluated. Cases with a basal serum LH level>0.2 mIU/L were considered to have an activated HPG axis based on clinical findings. A standard stimulation test with Gonadotropin-releasing hormone (GnRH) (Gonadorelin Acetate, LH-FSH 0.1 mg/mL; Ferring, Istanbul, Turkey) was administered intravenously at 100 mg in the morning, and serum LH and FSH levels were measured at 0, 30, 60, and 90 minutes. A peak LH of ≥5.0 mIU/L was considered indicative of HPG axis activation. Bone age was assessed using the Greulich and Pyle method.[5]

Pelvic USG was performed by an experienced radiologist to measure the long axis of the uterus and the double thickness of the endometrium. Cases with a uterine long axis >35 mm were evaluated as CPP based on clinical findings.[5]

Ethical Approval

The research has complied with all the relevant national regulations and institutional policies, is in accordance with the tenets of the Helsinki Declaration and has been approved by the Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (2024/4316). Written informed consent was obtained for all participant's legal guardians.

Statistical Analysis

Analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY). Numbers, percentages, means, medians, etc., were used to summarize the results. The normal distribution of numerical data was assessed using the Shapiro-Wilk test. For normally distributed data, mean and standard deviation (SD) were reported, while median and interquartile range (IQR) were used for non-normally distributed data. Differences between groups and parametric data were compared using the Student's t-test. Non-parametric data were compared using the Mann-Whitney U test. Categorical data were compared using the chi-square test or Fisher's exact test. Variables found significant in univariate analysis ($p<0.05$) were included in multivariate logistic regression analysis to identify independent effective

factors. The diagnostic performance of factors significant in multivariate analysis were further evaluated using receiver operating characteristic (ROC) curves. The Youden index were calculated as sensitivity - (1-specificity) from the coordinates of the curve. All p-values were evaluated bidirectionally, with p<0.05 considered significant.

Results

The median age was 7.1 years (range 5-8 years). The median birth weight was 3100 grams (IQR 2750-3406), and 61 patients (15%) were classified as SGA. At the time of presentation, the median weight was 0.9 SDS, the median height was 0.8 SDS, and the median BMI was 0.96 SDS. Obesity was observed in 19.4% of the cases (n=79). Among the patients, 252 were classified as SP-CPP, and 154 as RP-CPP. There were no significant differences in demographic and anthropometric data between these two groups (Table 1).

When the pubertal examinations at the initial presentation were evaluated, the median stage of thelarche was 2 (IQR 2-3), and the median stage of pubarche was 2 (IQR 1-2). The laboratory and radiological features showed that the LH, FSH, E2, and peak LH values in the SP-CPP group were 0.6 (IQR 0.4-0.9) mIU/L, 2 (IQR 1.2-3) mIU/L, 5 (IQR 5-14.9) pg/mL, and 4.1 (IQR 3.4-5.9) mIU/L, respectively. In the RP-CPP group, these values were 0.8 (IQR 0.5-2.2) mIU/L, 2.5 (IQR 1.6-4.6) mIU/L, 10 (IQR 5-23.8) pg/mL, and 5 (IQR 3.6-7.5) mIU/L, respectively. All hormone levels in the RP-CPP group were statistically significantly higher than those in the SP-CPP group (p<0.001, p<0.001, p=0.003, and p=0.002, respectively) (Table 2).

Table 1. Demographic and clinical features of the participants

Variables	All patients (n=406)	SP-CPP (n=252)	RP-CPP (n=154)	p
Age (years, median, range)	7.1 (5-8)	7.2 (5-8)	7 (5-8)	0.352[a]
Birth weight (gr, median, IQR)	3100 (2750-3406)	3100 (2747-3400)	3075 (2787-3425)	0.769[a]
Presence of SGA (n, %)				
Absent	345 (85)	217 (86.2)	128 (83.2)	0.412[b]
Present	61 (15)	35 (13.8)	26 (16.8)	
Weight SDS (median, IQR)	0.9 (0.3-1.5)	0.9 (0.29-1.55)	0.9 (0.3-1.5)	0.855[a]
Height SDS (median, IQR)	0.8 (0.23-1.4)	0.79 (0.24-1.49)	0.83 (0.22-1.37)	0.792[a]
BMI SDS (median, IQR)	0.96 (0.28-1.76)	1 (0.32-1.82)	0.91 (0.22-1.66)	0.432[a]
Presence of obesity (n, %)				
Absent	327 (80.6)	202 (80.2)	125 (81.2)	0.803[b]
Present	79 (19.4)	50 (19.8)	29 (18.8)	

[a]Mann-Whitney U-test; [b]Chi-square test; BMI: Body mass index; GnRH: Gonadotropin Release Hormone; IQR: Interquartile range; N/A: Non-applicable; RP-CPP: Rapidly progressive central precocious puberty; SDS: Standart deviation score; SGA: Small for Gestational Age; SP-CPP: Slowly progressive central precocious puberty.

Table 2. Puberty stage, laboratory and radiologic findings

Variables	All patients (n=406)	SP-CPP (n=252)	RP-CPP (n=154)	p
Tanner puberty stage (median, IQR)				
Thelarche	2 (2-3)	2(2-2)	3(2-3)	**0.001[a]**
Pubarche	2 (1-2)	2(1-2)	2(1-3)	0.488[a]
LH (mIU/L, median, IQR)	0.7 (0.4-1.4)	0.6 (0.4-0.9)	0.8 (0.5-2.2)	**<0.001[a]**
FSH (mIU/L, median, IQR)	2.2 (1.3-3.9)	2 (1.2-3)	2.5 (1.6-4.6)	**<0.001[a]**
Estradiol (pg/mL, median, IQR)	6.5 (5-20.3)	5 (5-14.9)	10 (5-23.8)	**0.003[a]**
Peak LH value (mIU/L, median, IQR)	4.5 (3.5-5.9)	4.1 (3.4-5.9)	5.7 (5-7.5)	**0.002[a]**
BA/CA (median, IQR)	1.14 (1-1.28)	1.12 (1-1.22)	1.25 (1.14-1.4)	**<0.001[a]**
Uterine length (cm, median, IQR)	34 (30-38.3)	33 (30.6-38.2)	35.1 (34-39.7)	0.442[a]
Endometrium thickness (mm, median, IQR)	1.75 (0.75-2.3)	1.6 (0.7-2.3)	1.8 (0.8-2.3)	0.813[a]
Height velocity SDS (median, IQR)	1.04 (0.16-2.51)	0.56 (-0.29-1.58)	1.46 (0.4-3.22)	**0.006[a]**

[a]Mann-Whitney U-test; BA/CA: Bone Age/Chronological Age; BMI: Body mass index; FSH: Follicle stimulating hormone; GnRH: Gonadotropin Release Hormone; IQR: Interquartile range; LH: Luteinizing hormone; N/A: Non-applicable; RP-CPP: Rapidly progressive central precocious puberty; SDS: Standart deviation score; SGA: Small for Gestational Age; SP-CPP: Slowly progressive central precocious puberty; All p-values less than 0.05 was bold.

The BA/CA ratio was a median of 1.12 (IQR 1-1.22) in the SP-CPP group and a median of 1.25 (IQR 1.14-1.4) in the RP-CPP group, showing a statistically significant higher ratio in the RP-CPP group (p<0.001). The pelvic USG measured the median uterine length for all patients at 34 mm (IQR 30-38.3), and the median endometrial thickness at 1.75 mm (IQR 0.75-2.3), with no significant differences between the two groups (p=0.442 and p=0.813, respectively) (Table 2).

There was a significant difference in the height velocity standard deviation (HVSD) between RP-CPP and SP-CPP groups, with SP-CPP having a lower HVSD compared to the RP-CPP group (p=0.006) (Table 2).

When the effects of being SGA or AGA on Tanner pubertal stage, LH, FSH, and estradiol levels, BA/CA ratio, and growth velocity were evaluated, no statistically significantly differences were observed between the two groups (Table 3). Among patients with SGA, those classified as RP-CPP had significantly higher LH and FSH levels and BA/CA ratios compared to those with SP-CPP (Table 4).

Tanner telarche stage, Luteinizing hormone, FSH, E2, peak LH value and BA/CA, which were significant in univariate analysis, were included in a binomial logistic regression analysis. In the multivariate analysis, Telarche stage (Odds ratio [OR]: 3.855, 95%-Confidence Interval [CI]: 1.704-8.719, p=0.001) and the BA/CA ratio remained significant (OR: 141.138, 95%-CI: 32.884-605.761, p<0.001), while the other parameters were loses their significance (Table 5).

Table 3. Distribution of laboratory and radiological parameters according to SGA or AGA status

Variables	All Patients (n=406)	SGA (n=61)	AGA (n=345)	p
Puberty stage (median, IQR)				
Breast	2 (2-3)	2 (2-3)	2 (2-3)	0.475[a]
Pubic	2 (1-2)	2 (1-2)	2 (1-2)	0.494[a]
LH (mIU/L, median, IQR)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	0.514[a]
FSH (mIU/L, median, IQR)	2.2 (1.3-3.9)	2.2 (1.2-2.9)	2.2 (1.3-3.9)	0.055[a]
E2 (pg/ml) (median,IQR)	6.5 (5-20.3)	5 (5-14.8)	7.6 (5-21.2)	0.184[a]
BA/CA (median, IQR)	1.14 (1-1.28)	1.13 (1-1.25)	1.14 (1-1.29)	0.777[a]
Height Velocity SDS (median, IQR)	1.04 (0.16-2.51)	1 (0.14-2.3)	1.1 (0.2-2.72)	0.749[a]

[a]Mann Whitney U test; AGA: Appropriate for gestational age; BA/CA: Bone age/Chronological age; E2: Estradiol; FSH: Follicle stimulating hormone; IQR: Interquartile range; IU: International unit; LH: Luteinizing hormone; SDS: Standart derivation scores; SGA: Small for gestational age; All p-values less than 0.05 was bold.

Table 4. Distribution of Laboratory and Radiological Parameters in SGA Cases According to Rapid and Slow Puberty

Variables	SP-CPP (n=35)	RP-CPP (n=26)	p
Puberty Stage (Median, IQR)			
Breast	2 (1-2)	2 (2-3)	0.080[a]
Pubic	2 (1-2)	2 (1-2)	0.285[a]
LH (mIU/L, Median, IQR)	0.62 (0.4-1.2)	0.95 (0.64-1.97)	**0.047[a]**
FSH (mIU/L, Median, IQR)	1.73 (0.99-2.67)	3.13 (1.78-5.62)	**0.014[a]**
E2 (pg/ml) (Median,IQR)	5 (5-10)	6.3 (5-23.9)	0.184[a]
BA/CA (Median, IQR)	1.1 (1-1.16)	1.21 (1-1.37)	**0.016[a]**
HV SDS (Median, IQR)	0.42 (0.22-1.5)	0.91 (0.06-2.63)	0.425[a]

[a]Mann Whitney U test; BA/CA: Bone age/Chronological age; E2: Estradiol; FSH: Follicle stimulating hormone; HV: Height velocity; IQR: Interquartile range; IU: International unit; LH: Luteinizing hormone; RP-CPP: Rapidly progressive central precocious puberty; SDS: Standart derivation scores; SP-CPP: Slowly progressive central precocious puberty; All p-values less than 0.05 was bold

Table 5. Multivariate Analysis of Factors Influencing progression rate of precocious puberty

Variables	Odds ratio	Lower (95%-CI)	Upper (95%-CI)	p
Tanner puberty stage (telarche)	3.855	1.704	8.719	**0.001**
LH	1.085	0.909	1.294	0.368
FSH	1.058	0.952	1.174	0.295
Estradiol	1.007	0.993	1.021	0.312
Peak LH value	1.001	0.990	1.012	0.858
BA/CA	141.138	32.884	605.761	**<0.001**

Binomial logistic regression analysis; Ref: Reference, 95%-CI: 95% Confidence interval; All p-values less than 0.05 was bold.

The effect of BA/CA, identified as an independent variable, in evaluating the speed of precocious puberty development was assessed using a receiver operating characteristic (ROC) curve. A BA/CA higher than the 1.18 cut-off value predicted RP-CPP with 69.5% sensitivity and 69.4% specificity (Area under the curve: 0.727, p=0.001) (Fig. 1).

Discussion

Central precocious puberty can exhibit either slow or rapid progression patterns. The rapidly progressing form often necessitates GnRHa therapy due to the potential for accelerated bone maturation, physical maturation, and early menarche.

In this cohort, when comparing the RP-CPP group receiving GnRHa treatment to the SP-CPP cases, the treatment group

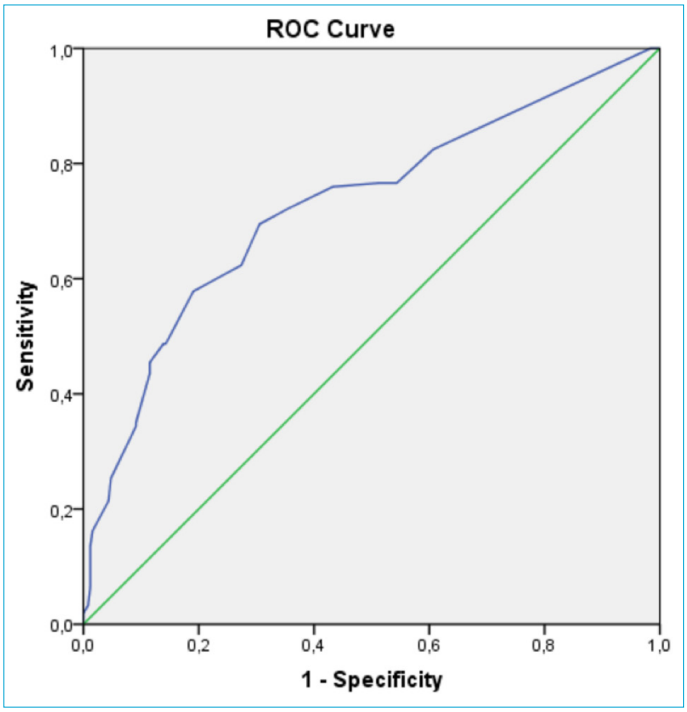

Figure 1. Receiver operating characteristic curve analysis for prediction of precocious puberty based on bone age/chronological age.

exhibited more advanced pubertal findings. Demirkale et al.'s study also observed that the RP-CPP group had more advanced breast development, although the pubic hair stage was similar between the two groups.[3] In this cohort, the thelarche stage in the SP-CPP group was significantly lower compared to the RP-CPP group, whereas there was no significant difference in pubic hair stages.

Nutritional habits, sedentary lifestyle, increased use of digital devices, and the resultant rise in obesity prevalence are factors influencing the development of CPP.[6] Chen et al. (2017) found a correlation between obesity and precocious puberty, identifying obesity as a contributing factor to CPP development.[7] Zeng et al. reported higher BA/CA in obese and overweight CPP children compared to those with normal weight, although laboratory parameters were similar.[8] In this cohort, 19.4% of CPP cases were obese, with obesity rates being comparable between the SP-CPP and RP-CPP groups.

It is known that SGA individuals have an increased risk of developing CPP compared to AGA individuals.[9] SGA individuals experience faster pubertal progression and may achieve a shorter final height.[10] Persson et al. highlighted that intrauterine exposures influence the onset of puberty, with SGA girls experiencing puberty and menarche approximately 5 months earlier than AGA girls.[11] Demirkale et al. reported similar menarche onset ages between SGA and AGA groups in SP-CPP cases.[3] Yu et al. found no differences in LH, FSH, and E2 levels between SGA and AGA CPP cases.[12] Our study, in line with the literature, found that 15% of CPP cases were SGA. Although laboratory variables were similar between the SGA and AGA groups, significant differences in LH, FSH, and BA/CA were observed between SGA-born SP-CPP and RP-CPP groups, with higher values in the SGA RP-CPP group.

Previous studies have indicated that GnRHa treatment provides no height benefits for girls with SP-CPP, consistent with the expectation that potential height gain is lost when bone age matures rapidly.[13] By definition, girls with a lower BA/CA ratio experience slower pubertal progression. Klein et al. demonstrated that a decrease in BA/CA is associated with delayed menarche onset and serves as a good indicator of pubertal suppression in treated girls.[14] Klein et al. showed a significant reduction in BA/CA in CPP cases receiving GnRHa treatment.[15] Some authors suggest making height-based treatment decisions for CPP girls undergoing GnRHa therapy. Adan et al. proposed treatment criteria based on predicting adult height (PAH) <155 cm and/or a LH/FSH peak ratio>0.6, observing greater breast development, advanced BA (2.0±0.2 years), and higher plasma E2 concentrations in the treatment group.[16] Léger et al. based treatment decisions on BA and peak LH, not treating those with less than 2 years of BA advancement and peak LH <6 mIU/mL, but initiating treatment if PAH declined and a final height exceeding PAH and TH was achievable.[17] Thus, BA advancement and its close association with PAH are critical determinants for GnRHa therapy decisions. Varimo et al. emphasized the importance of closely monitoring growth velocity and BA.[18] Kutlu et al. classified cases with a BA/CA>1.2 as rapidly progressing.[19] Demirkale et al. demonstrated in their study on final height that the BA/CA ratio in RP-CPP cases is higher compared to those with slower progression.[3] Our study suggests that a BA/CA ratio above 1.18 may serve as a predictive value for rapidly progressing puberty. While our study does not explicitly address the benefits of GnRHa therapy on final height and menarche age for children with a BA/CA ratio at this threshold, we believe early identification of RCPP can provide clinical benefits.

The main limitations of our study include its retrospective design and the relatively small sample size. Moreover, the lack of follow-up until final height represents a major limitation in assessing the long-term efficacy of GnRHa treatment. Furthermore, the comparable proportion of obese patients in both groups limits the ability to assess the impact of obesity. Another limitation of our study is the inability to evaluate family history and maternal or sibling age at menarche due to incomplete records.

Conclusion

The slow and rapidly progressing forms of CPP can be distinguished through clinical, laboratory, and bone age assessments. While SCPP generally follows a milder clinical course, RCPP requires more aggressive treatment. It is crucial to classify early puberty cases by their progression patterns through a combined evaluation of clinical, laboratory, and radiological findings, and to make individualized therapeutic decisions regarding GnRHa therapy. Understanding the tempo of puberty progression is vital in treatment decisions, and we believe that the BA/CA ratio can serve as a valuable guide in this context.

Disclosures

Ethic Committee Approval: The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (date: 27.02.2024 number:4316).

Informed Consent: Written informed consent was obtained for all participant's legal guardians.

Conflict of Interest: The authors declared that have no conflict of interest.

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