Zeynep Kamil Med J 2021;52(2):96–101
DOI: 10.14744/zkmj.2021.10337

ORIGINAL ARTICLE

Evaluation of etiological, laboratory, and anthropometric characteristics of patients treated with the diagnosis of precocious puberty

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ABSTRACT

Objective: This study aimed to determine the etiological distribution of patients treated for precocious puberty and to compare the results of gonadotropin-releasing hormone (GnRH) analog treatment with clinical and laboratory data during the administration and follow-up period.

Material and Methods: The files of patients treated with a diagnosis of precocious puberty between October 2016 and July 2019 in the pediatric endocrinology outpatient clinic were retrospectively analyzed.

Results: While 39 (88.6%) of our patients with precocious puberty were female, five (11.4%) were male. True precocious puberty (TPP) was found in 42 patients (95.5%) and combined precocious puberty (CPP) in two patients (4.5%). While 37 (88.1%) of TPP patients were diagnosed with idiopathic precocious puberty, an organic cause was found in five patients. Both of the patients treated for CPP had late-onset congenital adrenal hyperplasia. The mean estimated adult height (EAH) before the treatment was 151.88±6.77 cm in our patients between the ages of 6 and 8 who were started on GnRH analog treatment with a diagnosis of TPP, while the mean EAH after treatment was 155.16±7.82 cm ($p<0.001$). An increase in body mass index-standard deviation score was found in patients who received triptorelin acetate treatment, but no statistically significant difference was found.

Conclusion: Precocious puberty is more common in girls, and idiopathic TPP constitutes the majority of cases. GnRH analog treatment may contribute positively to the EAHs of girls with TPP, especially those younger than 8 years old.

Keywords: Combined precocious puberty, estimated adult height, gonadotropin-releasing hormone analogs, true precocious puberty

This study was presented orally at the Health Growing Child Online Congress.

Cite this article as: Bolu S, İşleyen F, Danış A. Evaluation of etiological, laboratory, and anthropometric characteristics of patients treated with the diagnosis of precocious puberty. Zeynep Kamil Med J 2021;52(2):96–101.

Received: December 09, 2020 **Accepted:** February 21, 2021 **Online:** June 20, 2021
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INTRODUCTION

Puberty includes physical, mental, and social changes in the transition from childhood to adulthood. Puberty is the developmental period in which secondary sex characteristics emerge with the onset of spermatogenesis in boys, ovulation in girls, and reproductive ability is acquired.[1] Precocious puberty is the onset of secondary sex characteristics before the age of eight in girls and nine in boys. The age of onset of puberty may vary according to environmental factors such as genetic and ethnic characteristics, socioeconomic factors, nutritional status, and geographical location.[2]

Precocious puberty is physiopathologically classified as true precocious puberty (TPP) (gonadotropin dependent/central) and peripheral precocious puberty (gonadotropin independent/pseudo). TPP is more common in girls than in boys, and it is always isosexual since pubertal findings always correspond to gender. The emergence of secondary sex characteristics with early activation of the hypothalamic-pituitary-gonad (HHG) axis is defined as TPP. While cases of TPP in girls are mostly idiopathic, organic causes of TPP are more common in boys. Pseudo-precocious puberty (PPP) is defined as precocious puberty in which secondary sex characteristics appear without normal HHG interaction, and isosexual or heterosexual development is observed. The addition of TPP as a result of the stimulation of long-term endogenous sex steroids to some diseases such as McCune-Albright Syndrome, which is a cause for PPP, congenital adrenal hyperplasia (CAH), which could not be treated sufficiently and in time, is defined as combined precocious puberty (CPP).[3]

Treatment in precocious puberty is aimed at the underlying cause. Early secretion of estradiol in cases diagnosed with TPP shortens the growth period and causes a shorter final height. A decrease in estradiol secretion is achieved by suppressing the pituitary-gonad axis with gonadotropin-releasing hormone (GnRH) analogs. Thus, bone age progression slows down, and the growth potential is maintained.[4]

This study aimed to determine the etiological distribution of patients treated for precocious puberty in the pediatric endocrinology clinic and to compare the results of GnRH analog treatment with clinical and laboratory data during the application and follow-up period.

MATERIAL AND METHODS

Forty-four patients treated with precocious puberty diagnosis between October 2016 and July 2019 in the pediatric endocrinology outpatient clinic were included in the study. Before the study, approval was obtained from the ethics committee of the relevant university with the decree dated May 21, 2019, and No 2019/4-22.

From the file information of the cases, gender, admission age, follow-up time, estimated adult height (EAH), treatment initiation age, duration of treatment, height, weight, body mass index (BMI), and standard deviation score (SDS) values at admission and follow-up, bone age (BA), pelvic USG, cranial-pituitary MRI results, and laboratory findings were recorded. In the pelvic USG, the anteroposterior diameter of the uterus and the ovarian dimensions, if viewable, were measured.

According to their BMI percentiles, the cases were evaluated and grouped as underweight if <5%, normal weight between 5–85%, overweight 85–95%, and obese if >95%. Data from Turkish children were used for weight and height SDS measurements.[5] BA was determined according to the Greulich Pyle method by taking radiographs of the left hand-wrist in all cases at the time of diagnosis. Puberty staging was done as per the Tanner Criteria. Testicular volume in men was determined by Prader Orchidometer. Baseline serum LH and FSH and estradiol (E_2)/total testosterone (TT) levels and, when necessary, luteinizing hormone-releasing hormone (GnRH) stimulation test was performed in the cases, and LH/FSH levels were examined at 0th, 20th, and 40th min.[6]

Serum hormone levels were studied in the Maternity and Children's Hospital Additional Service Building Laboratory. Immunochemiluminescent (ICMA) method was used to measure LH and FSH levels, while the radioimmunoassay (RIA) method was used to measure 17-hydroxyprogesterone (17OHP) and 1,4-delta androstenedione, and chemiluminescent microparticle enzyme method was used to measure serum E_2 and TT levels.

The onset of breast development before the age of 8 in girls and an increase in testicular volume above 4 ml before the age of 9 in boys was accepted as precocious puberty. Bone age at least 1 year older than the calendar age (CA), baseline LH of ≥0.3 or the highest LH examined by chemiluminescence immunoassay method reaches 5 mIU/mL after intravenous injection of exogenous GnRH, when examined by ultrasound, uterine long axis reaching ≥35 mm and/or ovarian volume of ≥2 mL were defined as findings supporting TPP.[6] High levels of TT or E_2 were defined as PPP, although baseline and stimulated gonadotropin levels were suppressed in children whose secondary sex characteristics started before the age of 8 in girls and 9 in boys.

The addition of TPP to PPP (late-onset CAH, McCune Albright syndrome, and familial testotoxicosis) was accepted as CPP. Patients admitted with premature adrenarche and a baseline 17OHP value of >10 ng/ml were diagnosed with late-onset CAH.[7] Genetic analysis was planned with the same diagnosis in cases with a baseline 17OHP value of between 2 and 10 ng/ml and if the stimulated 17OHP level was detected >10 ng/ml after the adrenocorticotropic hormone stimulation test. The cases were compared in terms of laboratory findings, and demographic and anthropometric characteristics according to their diagnoses.

Statistical Analysis

The data obtained in the study were evaluated with the SPSS 24.0 (SPSS Inc. Chicago, IL, USA) statistical program. The compliance of the variables to normal distribution was examined with the Kolmogorov–Smirnov Test. Intergroup differences were evaluated with Chi-square and Fisher's exact test. While variables showing normal distribution were evaluated between groups, they were analyzed with an independent-sample and paired-sample t-test. The cases where statistically $p<0.05$ was present were considered significant.

RESULTS

General Properties of the Cases

Thirty-nine (88.6%) of 44 patients who received GnRH analog treatment due to precocious puberty were female, while 5 (11.4%) were male. Precocious puberty rate was found to be 7.8 times higher in girls than boys. The mean age of diagnosis at the admission of the

Table 1: General characteristics of cases with true precocious puberty

	Female (n=44) Mean±SD	Male (n=5) Mean±SD
Calendar age (years)	7.17±0.80	8.12±0.50
Bone age (years)	9.18±1.78	11.00±1.50
BA-CA	1.65±0.88	2.50±0.90
BMI-SDS	0.63±0.89	0.13±1.19
Height-SDS	0.53±1.36	1.63±0.62
PAH (cm)	150.56±6.68	170.83±6.96
Duration of treatment (months)	20.37±16.82	12.00±7.57
Uterine longitudinal diameter (mm)	33.48±8.54	
Mean ovarian volume (cm^3)	1.71±1.03	
Basal FSH (mIU/mL)	3.95±2.50	2.65±1.50
Basal LH (mIU/mL)	1.13±1.14	0.21±0.20
Basal estradiol (pg/mL)	25.16±18.32	
Basal testosterone (ng/mL)		0.64±0.56
Peak FSH (mIU/mL)	17.89±7.93	7.23±2.27
Peak LH (mIU/mL)	17.62±17.84	12.03±6.65
Peak LH/FSH	0.25±0.18	0.93±0.09

BA-CA: Bone age-Calendar age; BMI: Body mass index; SDS: Standard deviation score; PAH: Predicted adult height.

cases was 7.2 years for girls and 8.1 years for boys. TPP was found in 42 (95.5%) of the cases, and CPP was found in 2 (4.5%). The number of patients diagnosed with TPP was 42 (38 girls, four boys), and 37 (88.1%) of these patients were idiopathic precocious puberty, while five patients had an organic cause.

In the TPP group, the BA in the admission was 9.1 years, 12 years in the CPP group on average, and the CA-BA difference in the TPP was 1.9 years and 3.3 years in the CPP group. General properties of our TPP cases are presented in Table 1.

When the cases were evaluated according to gender, 38 (97.4%) of the female cases had TPP and 1 (2.6%) had CPP, while 4 (80%) of the boys had TPP and 1 (20%) had CPP. Both patients with CPP were diagnosed with late-onset CAH.

While the result was normal in 22 (81.5%) of the patients who underwent cranial/pituitary MRI with a diagnosis of TPP, hydrocephalus was found in 2 (7.4%), macroadenoma in 2 (7.4%), and partially empty sella in 1 (3.7%). While TPP due to an organic cause was not detected in the male gender, all of our patients (5/5) were female, and the rate of TPP with an organic cause in girls was found to be 12.8%.

When our cases were evaluated in terms of BMI percentiles at admission, 26 female patients (66.7%) were thin and 13 patients (33.3%) were normal weight, while three male patients (60%) were thin and two patients (40%) were normal weight. There were more thin patients in both groups, but there was no statistically significant difference (p=0.563). No overweight or obese patients were found.

When the birth history of our patients diagnosed with precocious puberty was examined, it was found that 4 (9.1%) were born with intrauterine growth retardation (IUGR), and 3 (6.8%) were born with macrosomia.

When our patients were grouped in terms of age at initiation of treatment, four patients (9.1%) were under 6 years old, 26 patients (59.1%) were between 6 and 8 years old, and 14 patients (31.8%) were over 8 years old. While treatment was initiated in half of the patients (22/44) at the time of admission, treatment was initiated in the other half (22/44) during follow-up.

Complaint at Admission

In TPP cases, breast enlargement was present in 27 patients (64.2%), pubic hair growth in six patients (14.3%), vaginal bleeding in four patients (9.5%), penile enlargement in two (4.8%) patients, weight gain, and breast enlargement in two (4.8%) patients, and axillary hair growth in one patient (2.4%). The complaint at the admission of a patient with a CPP diagnosis was pubic hair growth, and the other was axillary hair growth.

Baseline Hormonal Evaluation

Mean baseline LH level in TPP cases was found as 1.12±1.14 mIU/ml, baseline FSH as 3.87±2.44 mIU/ml, and baseline E_2 as 25.14±18.57 pg/ml, and in the CPP group, the mean baseline LH level was found as 1.11±0.45 mIU/ml, baseline FSH as 6.94±6.51 mIU/ml, and baseline E_2 as 30.1±5.79 pg/ml, but no statistically significant difference was found between the two groups (p>0.05).

GnRH Stimulation Test Results

GnRH stimulation test was performed on application to 11 of our patients diagnosed with precocious puberty, and the mean peak FSH value was found as 13.62±8.18 mIU/ml, peak LH as 15.08±14.41 mIU/ml, and peak LH/FSH ratio as 1.24±0.90.

Hormonal Response to Treatment Given and GnRH Analog Treatment

Twenty-five of our patients diagnosed with real precocious puberty had received triptorelin acetate treatment, 17 of them leuprolide acetate treatment, one of our CPP patients had received triptorelin acetate and hydrocortisone, and the other had leuprolide acetate and hydrocortisone.

When the mean baseline LH, baseline FSH, and LH/FSH ratios were compared before and after treatment in our TPP cases, the mean baseline LH, FSH, and LH/FSH ratio after treatment was found to be significantly lower than before treatment (Table 2).

Comparison of TPP Cases Before and After Treatment in Terms of EAH

While the mean EAH of our cases before treatment was 151.91±7.35 cm, it was found to be 155.73±8.08 cm after treatment. Post-treatment EAH was higher and statistically significant compared to pre-treatment EAH (p<0.001). When the patients treated with triptorelin and leuprolide acetate were compared according to mean age of diagnosis and

Table 2: comparison of pre-treatment and post-treatment anthropometric and hormonal parameters of cases with true precocious puberty

	Pre-treatment	Post-treatment	%95 CI		p*
			Alt	Üst	
Height-SDS	0.49±1.22	0.62±1.25	-0.35	0.10	0.277
Weight-SDS	0.67±1.04	0.76±0.93	-0.27	0.08	0.305
BMI-SDS	0.57±0.93	0.61±0.83	-0.25	0.15	0.619
PAH-SDS	151.91±7.35	155.73±8.08	-5.05	-2.12	**<0.001**
LH (mIU/ml)	1.12±1.15	0.47±0.54	0.24	1.06	**0.003**
FSH (mIU/ml)	3.86±2.46	1.81±1.65	1.05	3.04	**<0.001**
LH/FSH	1.28±6.12	0.31±0.31	-1.06	2.99	0.342

Paired-Sample t-test; Parameters are shown as mean±standard deviation; CI: Confidence interval; * p<0.05; BMI: Body mass index; SDS: Standard deviation score; PAH: Predicted adult height.

treatment initiation, mean BA, and Tanner stages before treatment, no significant difference was found between the two groups (p>0.05).

The Effect of GnRH Analog Treatment Initiation Age on EAH

When the effect of treatment initiation age on EAH was compared, it was found that the mean EAH before treatment was 151.88±6.77 cm in our patients aged 6–8 years and 155.16±7.82 cm after treatment (p<0.001). In patients over 8 years of age, the mean EAH before treatment was 151.75±9.13 cm, and after treatment was 156.52±9.28 cm (p=0.009). When the patients were examined in terms of the age of treatment initiation, it was found that the contribution of starting treatment to EAH between the ages of 6 and 8 years was statistically higher than those who were started treatment above 8 years old (p<0.05).

The Effect of Treatment on Height SDS and BMI SDS Values

When the height SDS and BMI SDS values of the patients who received leuprolide acetate treatment before and after the treatment were compared, it was found that the mean height SDS increased and the BMI SDS decreased, but no statistically significant difference was found (p>0.05). In patients who received triptorelin acetate treatment, an increase in height SDS and BMI SDS was found after treatment, but no statistically significant difference was found (p>0.05).

DISCUSSION

Precocious puberty is seen in approximately one in every 5.000 children. Premature closure of the epiphyseal plates due to precocious puberty may adversely affect the height potential. Besides, precocious puberty can lead to negative psychological consequences.[6,8] It was reported in the literature that precocious puberty is observed approximately 10 times more frequently in girls than in boys.[8] In our study, 39 (88.6%) of the patients were girls, and 5 (11.4%) were boys, and precocious puberty was detected 7.8 times more frequently in girls.

In our study, the mean age of girls with precocious puberty was 7.2 years and 8.1 years for boys. Studies have reported that the age of precocious puberty diagnosis ranges from 6.6 to 7.6 years in girls and between 5.8 and 7.2 years in boys.[9–12] In our study, girls' mean age was generally consistent with the literature, while it was higher in boys. This finding was attributed to parents' late noticing of precocious puberty findings in boys.

In our study, 37 of 42 patients were diagnosed as TPP due to an idiopathic cause, and five due to an organic cause. When our cases were evaluated in terms of TPP etiology, the rate of organic causes in the female gender was 12.8%. In the literature, the rate of organic causes in girls with TPP has been reported as 10–20%,[13] and the findings of our study were evaluated per the literature. Cranial MRI detected partial empty sella in a female patient diagnosed with TPP, and literature review showed that precocious puberty might rarely accompany empty sella syndrome in patients with anterior pituitary hormone deficiencies.[14]

It is known that puberty shifts to early periods in cases with IUGR. In a meta-analysis study conducted by Deng et al.,[15] it was shown that IUGR is associated with precocious puberty and early menarche age, especially in girls. Consistent with the findings of this study, the rate of IUGR among girls with precocious puberty in our study constituted a substantial portion (8.7%) of the cases. Although the exact mechanism of the development of precocious puberty in cases with IUGR is unknown, it is thought that rapid postpartum growth and rapid increase in fat mass are effective in this process.[16]

Mogensen et al.[17] detected pathological MRI findings in 13 (6.3%) of 208 patients with TPP who underwent cranial imaging. MRI was performed in 27 patients, and pathological results were detected in five patients (18.5%) in our study. This result has been associated with a small number of patients. There are studies reporting that girls with high-fat mass and BMI have earlier and faster pubertal development.[18,19] Contrary to the literature, the absence of our overweight and obese patients in our study made us think that environmental factors should not be ignored in the etiology of precocious puberty and showed the need for studies to be carried out on the subject.

The fact that BA/CA ratio is more than 1.2 in cases followed up due to precocious puberty shows that TPP progresses rapidly.[20] In the study of Mogensen et al.,[7] the BA-CA difference was found to be 1.6. In our study, in cases with a diagnosis of TPP, the mean BA at admission was 9.1 years, 7.2 years for CA, and the difference between BA-CA was 1.9 years, and bone age was found to be advanced in accordance with the literature.

Gonadotropin level measurements are essential in determining whether the HHG axis is activated or not. The use of third-generation measurement methods such as immunofluorometric (IFMA) and ICMA increased the diagnostic value of baseline values in the diagnosis of precocious puberty. Kandemir et al.[6] showed that a baseline LH level of >0.3 has high sensitivity and specificity in indicating precocious puberty. In another study conducted, Vurallı et al.[21] reported that a baseline LH level of ≥0.65 IU/L could be used as a screening test to indicate TPP. However, at the onset of puberty, baseline LH levels may not always provide sufficient information about the HHG axis activation. Determining the peak LH level >5 mIU/ml and the LH/FSH ratio of >0.66 with the GnRH stimulation test performed in these cases is significant for TPP.[6,7] In our study, baseline LH, FSH, and E_2 were detected at prepubertal levels in 11 female patients admitted with early breast development, and a pubertal response was obtained to the GnRH stimulation test performed thereafter.

It was reported that when starting GnRH analog treatment before the age of 6, the treatment contributes to the height, the contribution is partial between the ages of 6 and 8, and starting treatment after the age of 8 does not contribute to the height.[22,23] Since we had a small number of patients under the age of six in our study, the treatment effect on height could not be evaluated in this age group. When we compared the patients between the ages of 6 and 8 and those older than 8, it was determined that the contribution of treatment to EAH in the 6–8 age group was more than those over 8 years old, and the treatment initiated at an early age contributed more to the patients per the literature.

The effect of GnRH analog treatment on BMI is still controversial. In addition to studies reporting that treatment increases BMI, there are also studies reporting that it does not cause a change in BMI or even causes a decrease.[24,25] In our study, a partial increase in BMI-SDS was detected after triptorelin acetate treatment. However, the increase in BMI-SDS was not found to be statistically significant.

CONCLUSION

Precocious puberty is more common in girls, and most of the cases are TPP cases. GnRH analog treatment may positively contribute to the EAH of girls with TPP, especially girls younger than 8 years old. More comprehensive studies are needed to evaluate the effects of treatment on body composition and adipose tissue.

Statement

Ethics Committee Approval: The Adıyaman University Clinical Research Ethics Committee granted approval for this study (date: 21.05.2019, number: 2019/4-22).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SB; Design – SB, Fİ; Supervision – Fİ, AD; Resource – SB; Materials – SB, Fİ; Data Collection and/or Processing – SB; Analysis and/or Interpretation – SB, AD; Literature Search – SB, Fİ; Writing – SB, Fİ; Critical Reviews – Fİ, AD.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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