Evaluation of Clinical Characteristics of Girls with Central Precocious Puberty at Diagnosis and During Treatment

Santral Puberte Prekokslu Kızların Tanı Anında ve Tedavi Süresince Klinik Özelliklerinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of this study is to evaluate the anthropometric and clinical characteristics of girls with idiopathic central precocius puberty (CPP) at diagnosis, during and at the end of treatment.

Material and Methods: Sixty-one girls who were diagnosed with CPP and treated between January 2015 and December 2018 were included in the study. The anthropometric, clinical characteristics and laboratory test results at diagnosis, during and at the end of treatment were evaluated retrospectively.

Results: Mean age of the patients at diagnosis was 8.7±0.6 years, bone age was 9.4±1.2 years, target height was 158.5±5.2 cm and predicted height was 159.1±6.9 cm. While 18 (30%) patients presented with isolated thelarche, 11 (18%) patients presented with menarche. At diagnosis, 28% of the patients were obese and 25% were overweight. The average treatment period was 2 years. The body mass index (BMI) increased during treatment ($p<0.001$), which was significant especially in the first two years of treatment ($p<0.001$). In the first year of treatment, the ratio of the obese patients had increased to 36%. During treatment, height growth rates were decreased ($p=0.02$). However, the predicted height at the end of the study was 160.1±6.2 cm and there was no difference when compared to the height at diagnosis ($p>0.05$).

Conclusion: Obese and overweight girls should be followed up for pubertal development. Awareness level of primary care physicians and pediatricians should be increased in order to identify the early puberty findings and provide appropriate guidance.

Key Words: Awareness, Idiopathic, Menarche, Obesity, Precocious puberty

ÖZ

Amaç: İdyopatik santral puberte prekokslu (SPP) kız olguların tanı anındaki, tedavi süresince ve tedavi bitimindeki antropometrik ve klinik özelliklerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya Ocak 2015-Aralık 2018 yılları arasında SPP tanısı alan ve tedavisi tamamlanan 61 kız hasta çalışmaya alındı. Hastaların tanı anında, tedavi süresince ve bitiminde antropometrik, klinik ve laboratuvar özellikleri geriye dönük incelendi.

Bulgular: Hastaların tanı anındaki ortalama yaşı 8.7±0.6 yıl, kemik yaşı 9.4±1.2 yıl, hedef boy 158.5±5.2 cm ve öngörülen boy 159.1±6.9 cm'di. Hastaların 18'i (%30) izole telarş ile başvururken 11'i(%18) menarş ile başvurduğu görüldü. Tanı anında hastaların %28'i obez ve %25'i fazla kiloluydu. Hastaların tedavi süresi ortalama 2 yıldı. Tedavi süresince hastaların vücut kitle indeksinde (VKİ) artış saptandı ($p<0.001$). Bu artış özellikle tedavinin ilk iki yılında belirgindi ($p<0.001$). Tedavinin 1. yılında obez hasta oranı %36'ya çıkmıştı. Tedavi süresince uzama hızlarında azalma saptandı ($p=0.02$). Ancak hastaların tedavi bitiminde öngörülen boyları 160.1±6.2 cm'di ve tanı anına göre farklılık yoktu ($p>0.05$).

Sonuç: Obez ve fazla kilolu kız çocukları pubertal gelişim açısından yakın takip edilmelidir. Özellikle erken puberte bulgularının tanınması ve uygun yönlendirme yapılması için bu konuda birinci basamak hekimlerinin ve pediatristlerin farkındalık düzeyinin artırılması gerekmektedir.

Anahtar Sözcükler: Farkındalık, İdyopatik, Menarş, Obezite, Puberte prekoks

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INTRODUCTION

Central precocious puberty (CPP) is the development of secondary sex characteristics before the age of 8 in girls and 9 in boys due to early activation of hypothalamus-pituitary-gonad axis (1). Although the incidence of CPP varies in different populations, its incidence is less than 2/10000 in females and 5/10000 in males (2). Nowadays, long-acting gonadotropin releasing hormone (GnRH) analogues are preferred in treatment of CPP due to their safe, effective applications and good patient compliance. GnRH analogues are in use since 1981 (3). The aim of this treatment is to delay epiphyseal closure by slowing bone maturation and to slow down / stop the progression of secondary sex characteristics by suppressing the pituitary-gonad axis (4). Although not frequent, systemic complaints such as headache, hot flashes, emotional and behavioral problems, seborrhea and acne can be seen. Approximately 10 to 15% of the patients have reported local side effects such as pain at injection site, rashes, sterile abscesses (5). Long-term side effects on reproductive system, bone health and body fat mass have been evaluated (6-8). There are many studies investigating the BMI in particular. It is not clear which mechanisms cause predisposition to overweight or obesity. Yet, there are studies showing that CPP treatment has different effects on BMI (9-12).

The aim of this study was to evaluate the anthropometric, clinical and laboratory findings of the girls diagnosed with CPP at the time of diagnosis, during and after treatment.

PATIENTS and METHODS

A total of 61 female patients who were diagnosed with idiopathic CPP and treated in department of pediatric endocrinology in Bursa Yuksek Ihtisas Education and Research Hospital between January 2015 and December 2018 were included in this sectional study. The Local Ethics Committee of the hospital approved the study protocol (nr: 2011-KAEK-25 2019/02-03) and the study was performed in accordance with Declaration of Helsinki. Patients who presented to the hospital with any signs of puberty were evaluated for CPP. The patient was diagnosed with CPP if; a) onset of breast development was before the age of 8, b) the growth rate was increased and the bone age was at least 1 year ahead of the calendar age, c) basal luteinizing hormone (LH) level was 0.3 μIU/ml and/or LH level after luteinizing hormone-releasing hormone (LHRH) stimulation was ≥5 μIU/ml (13, 14). Cranial magnetic resonance imaging (MRI) was performed in all patients to exclude cranial organic pathologies. Patients with brain tumor, history of cranial radiotherapy, congenital adrenal hyperplasia and hypothyroidism were excluded from the study.

Height, body weight (BW), BMI and standard deviation (SD) scores were calculated before treatment. Tanner staging was used to determine the puberty stage of the patients (15). Bone age was evaluated. The genetic height was calculated according to mother and father height. According to their presentations, patients were divided into groups as: breast development (thelarche), pubic and /or axillary hair (pubarche) and menstrual bleeding (menarche).

All patients were started with GnRH analogues [(Lucrin depot 3.75 mg® (leuprolide acetate) Decapeptyl depot 3.75 mg® (triptorelin acetate)]. The treatment was administered intramuscularly/subcutaneous every 28 days. The patients were evaluated every 3 months. Puberty findings, height, BW, BMI, growth rates were recorded. GnRH analogue test was performed to evaluate the pituitary-gonad axis suppression in patients with rapid clinical progression under treatment. Peak LH level <5μIU/ml showed suppression (16). Bone age was evaluated annually. The treatment was discontinued when the calendar age of the patients was 11 and/or bone age was 12 (17-19). Height, BW, BMI, puberty stage and bone age of the patients were recorded at the end of treatment. Duration of the treatment was calculated.

Height measurement was recorded in cm by using Harpenden Stadiometer. Body weight was measured on an empty stomach without top clothing and recorded in kg. Body mass index was calculated by weight (kg)/height $(m)^2$ formula. Height, BW, BMI scores and standard deviation were calculated. Patients with a body mass index of 85th-95th percentile were calculated as overweight and those with ≥95p were obese.

Target height (TH) was calculated by using the (mother height + father height)-13/2 formula (20). Bone age was evaluated by using the Greulich and Pyle atlas (21). The predicted height (PH) was calculated according to Bayleu and Pinneau method (22).

SPSS-21 software package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA) was used for statistical analyses. Data was mean±SD. Minimum and maximum values were given between parantheses. In the analysis of the data, the variance analysis of repeated measures and Friedman test were used. In case of significance, Wilcoxon signed rank test and paired t-test were used. $p<0.05$ was accepted for statistical significance.

RESULTS

A total of 61 females with idiopathic CPP were included in the study. The mean presentation age of the patients was 8.7±0.6 years. Twenty-nine (47%) patients presented with telarche and pubarche, 18 (30%) with thelarche, 11 (18%) with menarche and 3 (5%) with pubarche clinics (Figure 1). According to puberty staging, 46% of the patients were Tanner stage 3, 28% were stage 2 and 26% were stage 4. The pretreatment average BW of the patients was 31.2±5.6 kg, average height 131.9±4.0 cm, mean BMI 17.8±2.5 kg/m2. At diagnosis, 28% of the patients were obese and 25% were overweight. The pretreatment mean bone age was 9.4±1.2 years, target height

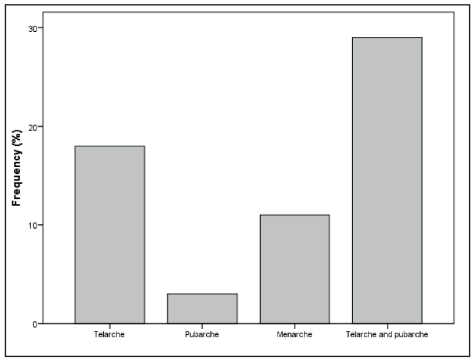

Figure 1: Presentation of Patients.

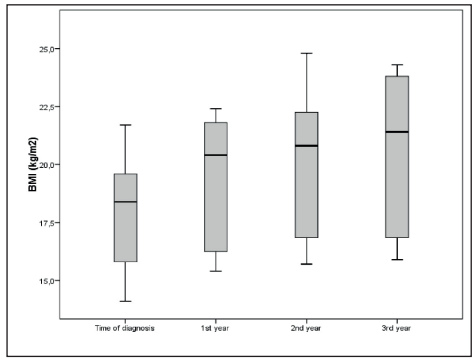

Figure 2: The changes in BMI levels according to treatment duration.

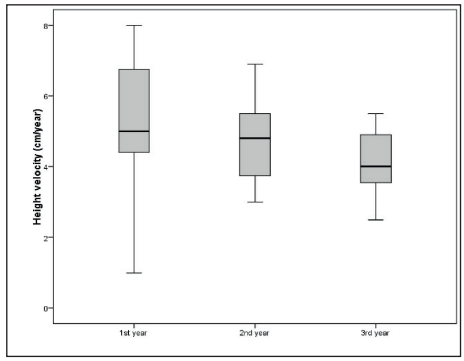

Figure 3: Height velocity of patients during treatment.

was 158.5±5.2 cm, PH was 159.1±6.9 cm. The pretreatment mean follicle stimulating hormone (FSH) levels were 4.9±2.1 µIU/ml, LH 1.9±1.8 µIU/ml and estradiol (E_2) 40.0±17.7 pg/ml. Average duration of treatment was 2 years. The clinical and laboratory findings of the patients before treatment are given in Table I. BMI was found to be increased during treatment ($p<0.001$). The rate of the obese patients had increased to 36% at the end of the first year of treatment. The changes in BMI levels according to treatment duration are shown in Figure 2. There was a significant increase in BMI levels during treatment when compared to the pretreatment term ($p<0.001$). BMI continued to increase during the ^{1}st and ^{2}nd years of treatment ($p=0.01$). Even though the increase continued in the ^{3}rd year of treatment, it was not statistically significant ($p>0.05$).

During treatment, the growth rates were 5.3±1.8, 4.8±1.2 and 4.0±0.9 cm for the ^{1}st, ^{2}nd and ^{3}rd years of treatment, respectively. The growth rate decreased during treatment ($p=0.02$) (Figure 3).

The bone age of the patients was 10.2±0.9, 10.9±0.9 and 11.5±0.8 years for the ^{1}st, ^{2}nd and ^{3}rd years of treatment, respectively. The predicted height was 159.2±6.2, 160.8±5.5 and 160.1±6.2 cm for the ^{1}st, ^{2}nd and ^{3}rd years of treatment, respectively. There was no significant difference between the bone age and the predicted height during treatment ($p>0.05$). The clinical characteristics of the patients during treatment are given in Table II.

Table I: Clinical and Laboratory Characteristics of Patients.

Number of patients *	61 (100)
Presentation of patients *	
Telarche	19 (30)
Pubarche	3 (5)
Telarche and pubarche	29 (47)
Menarche	11 (18)
Age at diagnosis (mean year ±sd)	8.7±0.6
Bone age (mean year ±sd)	9.4±1.2
Target height (cm)	158.5±5.2
Predicted height (cm)	159.1±6.9
Body weight (kg)	31.2±5.6
Body weight sd	0.8±1.0
Height (cm)	131.9±4.0
Height sd	0.6±0.7
BMI (kg/m²)	17.8±2.5
BMI sd	0.8±1.0
FSH (mIU/ml)	4.9±2.1
LH (mIU/ml)	1.9±1.9
E2 (pg/ml)	40.0±17.7
Duration of the treatment *	
1 year	14 (23)
2 years	38 (62)
3 years	9 (15)

Sd:*Standard deviation,* ***BMI:****Body mass index,* ***FSH:*** Follicle stimulating hormone, ***LH;****Luteinizing hormone,* ***E_2****:Estradiol,* *******: n(%)*

DISCUSSION

The onset of puberty in girls is clinically often thelarche. However, pubic hair may grow rarely before or together with thelarche (23). In the study, 47% of the patients presented with both thelarche and pubarche findings. In addition, 18% of the patients presented with menarche. The pubertal status was 46% Tanner stage 3, 28% stage 2 and 26% stage 4, respectively. This situation may be explained by the low level of awareness of the families about pubertal status. Most of the patients present to the hospital after the onset of menarche, which shows the seriousness of the condition. Early menarche has been associated with obesity, hypertension, type 2 diabetes, ischemic heart disease, stroke, estrogen-dependent cancer, and cardiovascular mortality (24,25). Biological, psychosocial and long-term health effects play a role in timing of puberty. In studies conducted in 1960s, the age range of onset of normal puberty has been determined as 8-13 years in girls (23). However, cross-sectional studies performed in the last 20 years show that onset of puberty is shifting to earlier ages. This situation can be explained by better health, nutrition and hygiene of people (26). The age of presentation of our patients was 8.7±0.6 years (7.5-9.8 years) and those presented with menarche in particular were in the older age group ($p<0.001$).

Table II: Clinical characteristics of patients during treatment.

	Time of diagnosis	1st year	2nd year	3rd year	p
Bone age (mean year ±sd)	9.4±1.2	10.2±0.9	10.9±0.9	11.5±0.8	<0.001[a,b,c]
Predicted height (cm)	159.1±6.9	159.3±6.2	160.8±5.3	160.1±6.2	>0.05[a,b,c]
Body weight (kg)	31.2±5.6	36.5±6.6	41.3±8.5	44.3±9.6	<0.001[a,b,c]
Body weight sd	0.7±1.0	0.8±1.11	0.9±1.13	0.7±1.1	>0.05[a,b,c]
Height (cm)	131.9±4.0	137.7±4.3	142.6±5.2	145.8±5.1	<0.001[a,b,c]
Height sd	0.6±0.7	0.7±0.7	0.4±0.8	0.1±0.7	>0.05[a,b,c]
Body mass index (kg/m²)	17.8±2.5	19.16±2.8	20.1±3.1	20.6±3.3	<0.001[a,b] >0.05[c]
Body mass index sd	0.8±1.1	1.1±0.9	1.0±0.8	0.7±1.0	>0.05[a,b,c]
Height velocity (cm/year)		5.3±1.8	4.8±1.2	4.1±0.9	<0.05[a,b,c]

*[a]:Comparison between 1st and 2nd years, [b]: Comparison between 1st and 3rd years, [c]: Comparison between 2nd and 3rd years standard deviation, **sd:** Standard deviation, parameters are shown as mean ± sd*

Before treatment, 28% of the patients were obese and 25% were overweight. Although it has been reported that the increase in body fat percentage in childhood is associated with early puberty, some studies have suggested that GnRH analogue therapy causes obesity.

BMI of the patients showed that 36% of the patients were obese and 23% were overweight in the 1st year of treatment. There is a significant increase in rate of obesity after treatment. In a study by Cruz et al. which have included 121 girls with CPP, the rate of the obese or overweight patients has been reported as 50.4% and at the end of the 1st year, they have found that this rate has increased to 70% (8). In another study including 176 girls with CPP, an increase in BMI has been detected after treatment, especially in patients who had a normal weight before treatment (27). In a study that has evaluated the body composition, it has been reported that body fat percentage has increased and lean body mass percentage has decreased during treatment (28). A similar study has shown that GnRH has caused significant increase in total fat mass without changing BMI (9). In contrast with these studies, there are many studies showing that GnRH treatment does not change BMI and BMI can be decreased with treatment (10, 12, 29).

Although a decrease in growth rates of patients was detected, there was no change in predicted heights. In a study that included 47 girls with CPP who were treated with GnRH and whose adult heights were evaluated, it has been shown that the adult height of the patients is taller than the predicted height (29). In a similar study that evaluated the adult height of 87 girls, it has been shown that adult height increase is significant in children younger than 5-6 years (10). In this study, the predicted and adult heights of the patients were not evaluated.

To conclude, obese and overweight girls should be monitored carefully for pubertal development. In order to identify the early puberty findings and provide appropriate guidance, awareness level of primary care physicians and pediatricians should be increased. Patients treated for CPP should be followed up for the increase in BMI.

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