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Effects of Gonadotropin-Releasing Hormone Agonist Therapy on Clinical and Laboratory Aspects of Patients with Central Precocious Puberty

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Abstract— Background: The primary goal of central precocious puberty treatment is to preserve final adult height. Safe and effective treatment of central precocious puberty in the form of long-acting GnRH analogs has been available for many years. **Aim of study:** To study the clinical characters of patients with central precocious puberty and their response to GnRh agonist therapy. **Patients and Method:** A randomized clinical trial study that conducted at Pediatric Endocrinology Outpatient Clinic in Children Welfare Teaching Hospital / Medical City from 1st of November 2018 to 30th of October 2019.Itincluded 83 patientspresented to the hospital because of early pubertal development and diagnosed with central precocious puberty. Subcutaneous injections of GnRH agonist (goserelin acetate [Zoladex]) were administered to all patients.Patients were observed for weight, height and sex maturation rate in addition to laboratory data were taken after at least 12 months. **Results:** In this study, there were significant decrease in height, suppression of the significant increase in bone age, and a significant increase in BMI level after treatment compared to that before treatment.Basal LH, FSH estradiol & testosterone values after treatment decline to significant levels. **Conclusion:** GnRHa treatment for CPP is safe and can be curative by improving the predicted height and delaying the growth rate.

Keywords: GnRHa, central precocious puberty, height, treatment, Iraq.

Introduction

In children,puberty is a complex transitional phase comprising of growth acceleration secondary sexual characteristics development(1). It is a multifactorial and a complex process that includes genetic, environmental,metabolic, geographic,ethnic, and economic factors whichleadsto the hypothalamic-pituitary-gonadal (HPG) axis reactivation (2).Pulsatile hypothalamic secretion of gonadotropin-releasing hormone (GnRH) is required for effective pubertal onset(3). Precocious puberty (PP) is classically defined as the development of secondary sexual characteristics before the age of eight years in girls and before nine in boys(4).It may be due to central or peripheral causes. Central precocious puberty (CPP) is driven by the GnRH and diagnosed if the development of physical pubertal changes and the hormonal profile are consistent with normal puberty, but just occur earlier that it should be. Globally, it difficult to estimate definitive numbers of cases as the prevalence and incidence vary significantly among different populations (5).Many studieshave cited a female to male ratio as high as 20:1(6). As a result of improved socioeconomic and socio-hygienic conditions, children's growth and development have been accelerated because of improvementsin nutrition and health (7). The number of childrenwith CPP is in the rise(8). Organic lesions with environmental factors and substrates that mimicked hormones(Endocrine disrupting chemicals) may have estrogen activity or may cause an increase of endogenous estrogen secretion, although the large majority of CPP is idiopathic. HPG axis can be disturbed by cosmetic products, foods

and some pharmacological insecticides which results in PP[9].Early onset of puberty and untreated PP might be linked to compromised adult height, increased prevalence of metabolic syndrome, dyslipidemia, dysglycemia, cardiovascular events, hyperandrogenism, increased risk of breast cancer, increased psychological disturbance, risk taking behavior and sexual activity[10].The primary goal of CPP treatment is to preserve final adult height[11].Safe and effective treatment of CPP in the form of long-acting GnRH analogs (GnRHas) has been available for many years[12]. Paradoxical down-regulation and suppression of the HPG axis is obtained by these drugs which are believed to work by providing a steady concentration of GnRH activity instead of the pulsatile variation in levels characteristic of native GnRHrelease [13].The aim of this study is to study the clinical characters of patients with CPP and their response to GnRhagonist therapy.

Patients and Methods

Study design,setting, and time: This wasa randomized clinical trial study that conducted at Pediatric Endocrinology Outpatient Clinic in Children Welfare Teaching Hospital/ Medical City in Iraq from 1st of November 2018 to 30th of October 2019.

Study Population and sample size: The study included 83 patients. All of them were children presented to the hospital because of early pubertal development and diagnosed with CPP. Any case of peripheral PP which convert to CPP like CAH &MacCune - Albright syndrome was also included in this study.All cases of peripheral PP which not convert to CPP, newly diagnose patients with CPP who need one year follow up duration, and any case of premature thelarche were excluded from the study.All the patients'parents signed an informed consent to participate and allows us to review their medical records for research purposes as long as the patient anonymity and confidentiality of their medical records are maintained. PP is defined as breast or pubic hair development at Tanner stage 2 or more before the age of 8 years and/or menses before the age of 9 years in girls and development of genitalia or pubic hair at Tanner stage 2 or more before the age of 9 years in boys[4].

Work-up: Data collection were done after history taking from patients' parents & file records. The following data were collected:age, gender, age at the time of onset of the complaint,and family history of similar conditions. All of the subjects underwent physical examination, based on physical findings and accelerated or not accelerated growth, decision was made for additional evaluations.

The body weight was measured using ground weight scale & height were measured using wall mounted stadiometer using the CDC data. Body mass index (BMI) was calculated by dividing the body weight to the square of the height in meters; height SD score was calculated as (height observed- mean height)/SD where height is the actual height of a child; mean and SD are the height and standard deviation of age corresponding to that child[14].

Pubertal staging at presentation (Tanner's stage) was assessed according to Marshall and Tanner of sexual maturation. Bone age was evaluated by X-ray of the left hand and wrist according to Tanner and white scoring system (TW2)[15].Hormonal assessment regarding basal FSH, LH, estradiol of females & testosterone of males' patients were measured using fully automated Chemiluminescence system in Institute of Educational Laboratories / Medical City & the detection limits for LH, FSH, estradiol &testosterone were depending on age of patients & laboratory normal values.Subcutaneous injections of GnRH agonist (goserelin acetate [Zoladex]) in dose of 3.6 mg every four weeks or 10.8mg every 12 weeks were administered to all patients.

Follow-up: After the initiation of GnRH agonist treatment, the patients were observed for weight, height and sex maturation rate with left-hand radiogram for the evaluation of BA in addition to laboratory data (basal FSH, LH, estradiol & testosterone) were taken after at least 12 months.

Statistical analysis: The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages.Paired t-test was used to compare the clinical and laboratory parametersbefore and after treatment.A level of P – value less than 0.05 was considered significant.

Results

In this study, the most common age of patients was > 6 years (53%); 79.5% of them were females; 6% had positive family history of PP as shown in table (1).

Table 1: Distribution of study patients by general characteristics

Variable	No. (n= 83)	Percentage (%)
Age (Year)		
<3	10	12.0
3 - 6	29	35.0
> 6	44	53.0
Gender		
Male	17	20.5
Female	66	79.5
Family history		
Yes	5	6.0
No	78	94.0

After treatment, there were significant decrease in height, suppression of the significant increase in bone age, and a significant increase in BMI level compared to that before treatment(0.26 versus 1.29 SD, P= 0.001; 10.2versus 8.4, P= 0.001; and 19.3 versus 16.36, P= 0.001 respectively).Regarding hormonal parameters, the basal LH, FSH estradiol &testosterone values after treatment decline to significant levels (1.7 versus5.7, P= 0.001; 3.2 versus 7.4, P= 0.002; 32.0 versus 97.8, P= 0.001; and 14.9 versus 25.4, P= 0.03 respectively) as shown in table (2).

Table 2: Comparison in clinical and laboratory parameters before and after treatment

Variable	Time		P - Value
	Before treatment Mean ± SD	After treatment Mean ± SD	
Clinical parameter			
Height (SD)	1.29 ± 2.0	0.26 ± 1.0	**0.001**
BMI (kg/m^2)	16.36 ± 3.0	19.3 ± 3.0	**0.001**
Bone age	8.4 ± 2.6	10.2 ± 2.4	**0.001**
Hormonal parameter			
LH (mU/ml)	5.7±8.5	1.7±3.1	**0.001**
FSH (mU/ml)	7.4±8.0	3.2±8.6	**0.002**
Estradiol (pg/mL)	97.8±74.1	32.0 ±26.5	**0.001**

Testosterone (ng/dl)	25.4±19.8	14.9±14.27	**0.03**

As shown in table (3), 75.9% of children showed suppressed heightafter treatment. Also, after treatment, BMI level was increased in 61.4% of them compared with the BMI at the beginning of treatment. At the end of treatment, 63.9% of childrenshowed clinical suppression of Tanner stage compared with pretreatment Tanner stage.

Bone age response to treatment till the last follow-up visit was observed in 62.7% of study patients and the highest proportion of children showed suppression in FSH,LH, estradiol & testosterone in response to GnRH agonist (67.5%, 73.5%, 74.3%, and 76.5% respectively).

Table 3: Distribution of study patients by clinical and laboratory findings according their response to treatment

Variable	No. (n= 83)	Percentage (%)
Height increment		
Decrease	63	75.9
Not Decrease	20	24.1
BMI increment		
Increase	51	61.4
Not increase	32	38.6
SMR response		
Respond	53	63.9
Not respond	30	36.1
Bone age response		
Respond	52	62.7
Not respond	31	37.3
FSH response		
Respond	56	67.5
Not respond	27	32.5
LH response		
Respond	61	73.5
Not respond	22	26.5
E2 response	**n= 66**	
Respond	49	74.3
Not respond	17	25.7
Testosterone response	**n= 17**	
Respond	13	76.5
Not respond	4	23.5

Discussion

Suppression of the gonadal sex steroid secretion effectively to stop premature sexual maturation is the main goal of CPP treatment. Moreover, it aims to suppress the accelerated skeletal advancement in order

to preserve the potential to achieve acceptable height in adulthoodof each individual [16]. If not treated, CPP results in short final stature if compared with the stature dictated by the child's genetic disposition[17]. The current study was conducted to evaluate the effect of GnRHa therapy.Evaluation was conducted using clinical and laboratory parameters and the difference between the initial and final parameters as outcome measures.

Results of this study showed a significant advantage for children with PP treated with GnRHa in terms of height, bone age, LH, FSH, E2, and testosterone. These results were in accordance with studies conducted by Lee S. J et al 2012, in Korea [18] and by Aguiar et al,2005 in Brazil [19] when they reported a significant decrease in height and increase in BMI level after one year of treatment. In other studies, GnRH agonist treatment didn't induce significant changes in BMI in CPP patients, and obesity was not related to GnRH agonist administration[18].The preponderance of evidence suggests that GnRHas don't have a negative effect on BMI in patients being treated for CPP[20]. It is difficult to determine whether increased BMI is a result of the therapy or is an expected manifestation of the primary disease process. This study agreed with results found by Kim YJ et al study, 2013 in Korea [21] in the findings regarding suppression of the increase in the bone age. The high value of bone age after treatment might be due to advance chronological age at time of collecting data in comparison at initial presentation before many years but the difference between chronological age & bone age at time of collecting data was minimum (about 1-2 years). The basal LH, FSH, E2 & testosterone values were declined to significant levels after treatment and this is similar to the finding reported by Neely EK et al study, 2011 in US [22]when showed significant decrease in LH, FSH, and testosterone after treatment.GnRHa exerts a highly inhibitory effect onhypothalamic pituitary gonadal axis torestrain the secretion of gonadotropin (LH and FSH),and stop gonad development, so the level of sexhormone declines[12]. In conclusion, GnRHa treatment for CPP is safe and can be effective in improving the predicted height and delaying the growth rate. Preventive measures, such as increased physical activity, can be introduced to minimize possible alterations in body weight, and a long-term follow-up study is required to elucidate whether GnRH agonist treatment in Iraqi patients with CPP affects adult obesity.Biochemical markers, bone age, and growth velocity should be followed during treatment to ensure efficacy.

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