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Original Article

J Clin Med Res. 2019;11(2):133-136

The Gonadotropin-Releasing Hormone Analogue Therapy May Not Impact Final Height in Precocious Puberty of Girls With Onset of Puberty Aged 6 - 8 Years

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Abstract

Background: The effect on final height of gonadotropin-releasing hormone analogues (GnRHa) used in the treatment of precocious puberty is controversial. The aim of this study was to determine whether or not GnRHa therapy would make any contribution to final height in precocious puberty of girls with onset of pubertal characteristic development aged 6 - 8 years.

Methods: Age at start of puberty, target height standard deviation score (SDS) presentation, follow-up height SDS, body mass index (BMI) SDS, bone age and predicted adult height of 34 female subjects who had reached their final height and with pubertal findings beginning at the ages of 6 - 8 were evaluated. These subjects were divided into two groups: treatment and non-treatment groups. The treatment group was further divided into two subgroups, receiving monthly or three-monthly depot GnRHa.

Results: Age at onset of puberty was 7.2 ± 0.9 years. Twenty-five cases were started on GnRHa and nine were followed-up without treatment. Fourteen cases received monthly 3.75 mg depot triptorelin acetate and 11 received three-monthly 11.25 mg depot. Mean age at start of treatment in the treatment group was 9.1 ± 1.2 years and mean bone age was 9.7 ± 2.3 years. Age at presentation in the non-treatment group was 8.4 ± 1.4 years and bone age was 10.3 ± 2.1 years. Target and final height SDS were similar in all the groups ($P > 0.05$). No difference was determined between the treatment groups in terms of initial height SDS, bone age, length of treatment, final height SDS or BMI SDS ($P > 0.05$).

Conclusions: GnRHa therapy did not make a positive contribution to final height in precocious puberty of girls with onset of puberty aged 6 - 8 years.

Manuscript submitted December 3, 2018, accepted December 20, 2018

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doi: https://doi.org/10.14740/jocmr3710

Keywords: Precocious puberty; Gonadotropin-releasing hormone analogue therapy; Final height; Bone age

Introduction

Central precocious puberty (CPP) can result in premature development of secondary sex characteristics and final height impairment derived from early fusion of the growth plates caused by accelerated bone maturation [1, 2]. CPP refers to the development of girls with onset of secondary sex characteristics before the age of 8 [3]. However, no single age range has been identified in moderately early puberty. Gonadotropin-releasing hormone analogues (GnRHa) have been used in the treatment of precocious puberty since 1980 [4]. The main aim in treating cases diagnosed with precocious puberty is to achieve normal adult height. Long-term contemporary studies report inconsistent results concerning variations in final heights between subjects receiving treatment and those not receiving treatment [5, 6]. Several factors have been shown to affect achievement of final height in cases treated with GnRHa. Various studies have reported the effects on final height of factors such as chronological and bone age at the beginning and end of treatment, length of treatment with GnRHa, decreased growth velocity during treatment, low predicted adult height (PAH), and target height [7, 8]. However, the number of randomized controlled studies investigating the effectiveness of treatment in precocious puberty is very low [9]. The purpose of this study was to determine whether or not GnRHa therapy would make any contribution to final height in precocious puberty of girls with onset of pubertal characteristic development aged 6 - 8 years.

Materials and Methods

Thirty-four female cases with pubertal findings beginning at 6 - 8 years and monitored with a diagnosis of CPP and who had reached their final height were investigated retrospectively. Age at onset of puberty, target height standard deviation score (SDS), pubertal findings at presentation and follow-up evaluated at 3-6-month intervals, height SDS, body mass index (BMI) SDS, PAH and bone age investigated once a year were

Table 1. Reference Oxology Evaluations of Study Groups

	Group 1	Group 2	P
Age	8.0 ± 1.6	8.4 ± 1.4	0.62
Height	138.7 ± 7.5	136.4 ± 9.6	0.52
Height SDS	1.3 ± 1.3	0.9 ± 1.3	0.54
PAH	165.4 ± 7.9	163.5 ± 8.1	0.51
PAH SDS	0.5 ± 1.3	0.4 ± 1.3	0.84
Bone age	9.7 ± 2.3	10.3 ± 2.1	0.69

SDS: standard deviation score; PAH: predicted adult height.

assessed. Subjects with a bone age of 15 or who had grown < 1 cm in the previous year were regarded as having reached their final height. Pubertal stages of the cases included in the study were assessed on the basis of the Tanner classification. Height and body weight measurements were taken in the morning using SECA 264 height and SECA 767 weight meters (Carson City, NV, USA). BMI was calculated using the formula kg/m^2. Subjects with a BMI SDS > 2 were considered obese. Height, weight and BMI were compared against standard curves for Turkish children [10, 11]. Bone age estimation was performed based on the Greulich-Pyle atlas from the left wrist in all cases. Bayley-Pinneau method was used for predicted adult height evaluation [12]. Target height and target height SDS were evaluated by measuring the height of the mother and father during outpatient follow-ups. Pituitary magnetic resonance imaging (MRI) was performed in all subjects in order to exclude potential organic pathologies. Subjects with thyroid hormone disorder, growth hormone deficiency, skeletal dysplasia, hydrocephaly, cerebral palsy, dysmorphic findings or accompanying chronic disease or chronic drug use that might affect growth and pubertal development were excluded.

Cases were divided into two groups: group 1 (N = 25), receiving treatment, and group 2 (N = 9), receiving no treatment. Fourteen of the treated cases received monthly 3.75 mg depot triptorelin acetate 75 - 100 µg/kg, while 11 received three-monthly 11.25 mg depot triptorelin acetate. Approval from the local ethical committee was obtained for the study.

Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences 22.0 statistical software program (IBM SPSS Statistics 22). Values are presented as means ± 2 standard deviations (SD) or median (range). Two-group comparisons were performed using the Mann-Whitney test. Normal distribution of data was evaluated using the Shapiro-Wilks test. P > 0.05 was regarded as compatible with normal distribution. Chi-square analysis was performed for categoric variables. The Wilcoxon matched two-sample test was used to define variation over time in the groups. Spearman's rho correlation was used for non-parametric correlation statistical analyses. A P value < 0.05 was regarded as significant for all tests.

Table 2. Height SDS and Delta Bone Age Values of the First and Second Years of the Study Groups

	Group 1	Group 2	P
First year height SDS	1.2 ± 1.4	1.3 ± 1.8	0.52
First year delta bone age SDS	0.7 ± 0.5	0.5 ± 0.8	0.96
Second year height SDS	1.1 ± 1.2	2.2 ± 0.5	0.10
Second year delta bone age SDS	0.77 ± 0.5	1.0 ± 0	0.20

SDS: standard deviation score.

Table 3. The Target Height and Final Height of the Study Groups

	Group 1	Group 2	P
Target height	158.4 ± 5.1	159.8 ± 5.8	0.40
Final height	157.4 ± 8.4	161.2 ± 7.4	0.16

Results

Twenty-five cases (73.5%) were started on GnRHa therapy (group 1), while nine (26.5%) were followed up without treatment (group 2). Patients of the treatment group received two different treatment regimens including 14 cases (56%) who received monthly 3.75 mg triptorelin acetate 75 - 100 µg/kg and 11 cases (44%) who received three-monthly 11.25 mg depot triptorelin acetate.

In the treatment group, mean age at presentation was 8.0 ± 1.6 years and pubertal stage was 2.8 ± 0.8, compared to 8.4 ± 1.4 and 2.5 ± 1.1 in the untreated group. Age at onset of puberty was 7.1 ± 1.0 years in the treatment group and 7.3 ± 0.5 in the untreated group. Height, height SDS, PAH, PAH SDS and bone age at presentation were similar between the two groups (P > 0.05) (Table 1).

Mean age of the subjects at onset of treatment was 9.1 ± 1.2, mean length of treatment was 2.1 ± 0.9 years and age at the end of treatment was 11.3 ± 0.8 years.

Cases' first and second year height SDS and delta bone age values are shown in Table 2. The mean difference between bone age and calendar age in the treatment group was 1.7 ± 1.2 years, and the first year bone age acceleration (delta bone age) was 0.7 ± 0.5 years.

In the treatment group, target height was 158.4 ± 5.1 and target height SDS was 0.5 ± 0.9, compared to 159.8 ± 5.8 and -0.4 ± 0.9 in the untreated group (P > 0.05). There was no significant difference between group target heights and final heights (Table 3). Deviation from target height SDS was 0.7 ± 1.3 SD in the treatment group and 0.9 ± 1.2 SD in the untreated group (P > 0.05). Nineteen cases included in the study achieved or exceeded their target height.

No difference was determined in terms of initial height SDS, bone age, length of treatment, final height SDS or BMI SDS values between groups receiving monthly 3.75 mg triptorelin acetate or three-monthly 11.25 mg depot triptorelin acetate treatment (P > 0.05).

No statistically significant difference in terms of BMI SDS was observed throughout observation between group 1 and

group 2 (P > 0.05).

Bone age at beginning of treatment was negatively correlated with final height SDS (P = 0.022, R = -0.457).

Discussion

While pubertal findings have been observed to emerge at earlier ages in some studies in the last 20 years, no negative impact has been determined on final height. In a study evaluating 15,439 girls by Herman-Giddens et al [13], age at onset of puberty was 7 - 8 years in 15% of cases. GnRHa are considered to increase final height in cases in which pubertal findings commence before the age of 6 [14]. Studies investigating the effect on final height of GnRHa therapy in girls with precocious puberty starting at 6 - 8 years have reported inconsistent findings, and the subject is still therefore a controversial one. In a study comparing cases of precocious puberty followed-up without treatment, Murram et al [15] reported that cases with pubertal findings commencing before 6 years remained shorter in stature than those in which pubertal findings commenced after the age of 6 years. A study by Kletter and Kelch observed no difference in final adult heights of treated and untreated cases in which pubertal findings began after 6 years [16]. Another study determined a marked difference in predicted adult final height and final height with GnRHa therapy in cases in which pubertal findings commenced at ages 6 - 8 [7]. A different study of 637 cases treated with GnRHa reported that the best response was achieved in subjects starting treatment at an early age, while GnRHa therapy was of no positive benefit in terms of height in cases treated at ages 8 - 10 [17]. Research has identified height at the beginning of puberty and target height as factors affecting final height [18]. We observed no significant difference in terms of final heights between treated and untreated cases diagnosed with precocious puberty which pubertal characteristic development beginning at ages 6 - 8 years. Delta bone age was similar during observation in treated subjects. A negative correlation was determined between bone age at start of treatment and final height SDS. Positive correlation was observed between final height and target height. Savas-Erdeve et al [19] reported that treatment with GnRHa in precocious puberty (pubertal findings beginning at 7 - 8.5 years) made no positive contribution to height, and emphasized that final height was affected only by target height and height at onset of puberty.

Cassio et al [20] in their study found that final height was equal to or exceeded target height in 14 out of 20 patients undergoing GnRHa therapy with onset of puberty at 7.5 - 8.5 years. Twelve out of 18 untreated patients achieved target height in that study. Positive correlation was determined in both groups between final height and height measured at initial examination and target height. In our study, 12 of the 25 treated patients and seven of the nine untreated patients achieved or exceeded their target height. No statistically significant difference was determined between deviation from target height SDS in the treated and untreated groups. Cassio et al [20] concluded that, similar to our own study, GnRHa was of no benefit to final height in precocious puberty.

Predicted adult heights were greater than final heights in our study. Final height calculations employing the Bayley-Pinneu system may be up to 13 cm higher in patients with central precocious puberty. It has therefore been concluded that the Bayley-Pinneu method cannot provide exact prediction of correct height in children with rapid bone growth progression [6, 21].

The optimal doses of GnRHa required to achieved hormonal suppression are still unknown. Monthly or three-monthly depot GnRHa is effective and safe in the treatment of precocious puberty. These results confirm that three-monthly injections may be a satisfactory alternative to monthly injections in the treatment of children with CPP [22]. Carel et al [23] achieved long-term pubertal suppression with 3.75 mg administration every 4 weeks in children with CPP. They also reported adequate gonadotropin suppression and sustained clinical utility with a 11.25 mg three-monthly depot [24]. We determined no difference between our treatment groups in terms of initial height SDS, bone age, length of treatment, final height SDS or BMI SDS values (P > 0.05).

Palmert et al [25] found that 41% of girls with central precocious puberty were overweight at time of diagnosis and that 22% were obese. However, their study also emphasized that no marked change was observed in BMI SDS throughout treatment. There is no information in the literature about the effect that GnRHa lead to obesity [25, 26]. In our study, also, the number of initially obese cases was 4 (11.7%). No marked variation was determined in BMI SDS in the treatment group.

In conclusion, this study compared anthropometric data of cases treated with GnRHa and cases monitored without treatment between the pubertal findings beginning at 6 - 8 years. GnRHa therapy did not make a positive contribution to final height in precocious puberty of girls with onset of puberty aged 6 - 8 years in this study. However, as for deciding on treatment in such cases, the best approach will be an individually-tailored regimen for each patient, and we also need to bear in mind the potential emotional effects. We think that the low number of cases included in the study is a factor that reduces its power. Prospective controlled studies involving a larger number of patients are now needed on this subject.

Conflict of Interest

The authors declare that there is no conflict of interest.

Financial Disclosure

None.

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