The Influence of GnRH Analog Therapy on Growth in Central Precocious Puberty

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Abstract

Background. Children with central precocious puberty (CPP) present various somatic and psychological abnormalities.

Objectives. The aim of the study was to evaluate growth changes in girls with central precocious puberty treated with GnRH analog therapy and to analyze the factors affecting the auxological response to this treatment.

Material and Methods. The study group consisted of 40 girls with puberty onset aged 6.0 ± 1.9 years (mean, ± SD), treated with 3.75 mg Decapeptyl depot intramuscularly every 28 days. The treatment was initiated at the age of 7.5 ± 2.2 years and continued for 3.3 ± 2.3 years, until the age of 11.4 ± 0.9 years. Height (Ht), height standard deviation score (HtSDS), statural age, bone age and Ht prediction.

Results. During the treatment a decline in HtSDS from 2.0 ± 1.36 to 1.24 ± 1.0 was observed (p = 0.0002); and a deceleration in the maturation of bones of 1.0 ± 0.29 year in the first year and 0.66 ± 0.33 year in the following years (p = 0.0008). The HtSDS at the end of the treatment was significantly higher than was predicted in pretreatment (1.33 ± 1.04 vs. 0.07 ± 1.39, p = 0.0005). Ht and HtSDS after treatment were positively correlated with the predicted Ht (PAH) before treatment and negatively correlated with the bone age/statural age ratio before treatment (p < 0.05). The PAH before and after treatment correlated inversely with the bone age/statural age ratio (p < 0.05).

Two subgroups were analyzed according to the patients’ age when therapy was introduced: group 1 included girls who were under the age of 7 when therapy was introduced, and group 2 included girls aged 7 or older. There was a statistically significant difference in the PAH SDS before treatment between these two subgroups: Group I (–) 1.3 ± 1.8 vs. Group II (–) 0.14 ± 1.2 and there was no difference in the PAH SDS after treatment: Group I (–) 0.7 ± 1.1 vs. Group II 0.31 ± 1.2.

Conclusions. The child’s age at the beginning of GnRHa therapy was an important predictor of height prognosis; the therapy introduced under the age of 7 improves the PAH during treatment. Height prediction during the entire treatment period is worse in children with more advanced bone age for their statural age at the onset of treatment (Adv Clin Exp Med 2016, 25, 1, 27–32).

Key words: growth, central precocious puberty, GnRH analog therapy.
Material and Methods

The Patients

The study was carried out on 40 girls with CPP in whom puberty started at the age 6.0 ± 1.9 years (mean, ± SD). All the patients had idiopathic CPP. The diagnosis of idiopathic CPP was based on:

1. The onset of thelarche and/or menses at a chronological age (CA) less than 8 years;
2. An accelerated growth rate;
3. Bone age (BA) more than one year over the CA, with a ΔBA/ΔCA ratio more than 1.2;
4. A pubertal response to GnRH stimulation, with a plasma LH peak greater than 10 IU/L and a stimulated LH/stimulated FSH ratio more than 1.0 [8];
5. Pubertal uterine size and ovarian development (revealed by pelvic ultrasonography) [9];
6. No evidence of hypothalamo-pituitary abnormalities in magnetic resonance imaging.

Primary adrenal or gonadal diseases and other conditions that might influence puberty and growth were excluded.

The characteristics of the patients treated with GnRHa are shown in Table 1.

The Treatment

All the girls were treated with the depot form of the GnRH analog triptorelin (decapetyl depot), Ferring Pharmaceuticals, Suffern, NY, USA), administered at a dose of 3.75 mg intramuscularly every 28 days.

After the CPP diagnosis, GnRHa treatment was initiated at the age of 7.5 ± 2.2 years, and was continued for 3.3 ± 2.3 years, until the age of 11.4 ± 0.9 years. Puberty suppression was confirmed by a GnRH stimulation test three months after the introduction of GnRHa treatment, and by evaluating basal LH, FSH and estradiol (E2) levels every six months during therapy. In all the patients the LH, FSH and E2 values were suppressed for the entire GnRHa treatment period.

The study design was accepted by the Ethics Committee of Wroclaw Medical University. A written informed consent was obtained from the parents of all the patients.

Methods

Height (Ht), height standard deviation score (HtSDS) and statural age, Ht prediction, body weight and bone age were evaluated before, during and after GnRHa therapy. Body height was measured every 28 days with a Harpender stadiometer [Holtain Ltd., Wales, United Kingdom]. HtSDS and statural age were calculated according to Polish growth standards. Ht predictions were calculated by the Bayley-Pinneau method. Weight was measured with an electronic scale every 28 days. The pubertal stage was evaluated in accordance with Marshall and Tanner [10]. Bone age was determined according to the Greulich and Pyle method every 12 months [11].

Serum LH and FSH were measured by lumino-immunoassay (Byk-Sangtec Diagnostica GmbH, Dietzenbach, Germany). Serum estradiol was measured by microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Uterine and ovarian volume and structure were evaluated by pelvic transabdominal ultrasonography using a 5-mHz Sonoline Prima device (Siemens Medical System, Inc. Ultrasound Group, Issaquah, WA, USA).

Statistics

The statistical analysis was done using STATISTICA 9 software (Statsoft Inc., Tulsa, OK, USA). Nonparametric tests were used: the Kolmogorov-Smirnov test, the Mann-Whitney U test and Spearman’s rank correlation coefficient. A p-value less than 0.05 was considered statistically significant.

Table 1. The characteristics (mean ± SD) of 40 patients with CPP before and after GnRHa therapy. The onset of puberty was at age 6.0 ± 1.9 years; the treatment period was 3.3 ± 2.3 years

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>At the end of therapy</th>
<th>P</th>
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<tbody>
<tr>
<td>CA (years)</td>
<td>7.5 ± 2.2</td>
<td>11.4 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>BA (years)</td>
<td>9.56 ± 2.14</td>
<td>12.4 ± 0.68</td>
<td></td>
</tr>
<tr>
<td>BMI SDS CA</td>
<td>1.1 ± 0.9</td>
<td>1.0 ± 0.9</td>
<td>ns.</td>
</tr>
<tr>
<td>Overweight prevalence (%)</td>
<td>9.8</td>
<td>18.6</td>
<td>ns.</td>
</tr>
<tr>
<td>Obesity prevalence (%)</td>
<td>22.0</td>
<td>14.0</td>
<td>ns.</td>
</tr>
<tr>
<td>HtSDS CA</td>
<td>2.0 ± 1.36</td>
<td>1.24 ± 1.0</td>
<td>0.0002</td>
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</tbody>
</table>

CA – chronological age; BA – bone age; BMI SDS CA – body mass index standard deviation score for chronological age; HtSDS CA – height standard deviation score for chronological age.
Results

Table I presents the characteristics of the patients on initiation and after discontinuation of the treatment.

A prompt regression or arrest of the clinical symptoms of puberty was observed during the entire treatment period (3.3 ± 2.3 years).

Bone age (BA) before treatment was 9.56 ± 2.14 years. After the GnRHa therapy was completed, BA was 12.4 ± 0.68 years.

During the treatment period a decline in HtSDS from 2.0 ± 1.36 to 1.24 ± 1.0 was observed (p = 0.0002) (Fig. 1). BA decelerated 1.0 ± 0.29 year during the first year and 0.66 ± 0.33 year in the following years (p = 0.0008) (Fig. 2). The mean HtSDS was significantly higher at the end of the treatment than the mean pretreatment predicted height (PAH) SDS (1.33 ± 1.04 vs. -0.07 ± 1.39, p = 0.0005). The mean HtSDS was also significantly higher at the end of the treatment than the mean HtSDS at the time of last visit after the end of the treatment (1.23 ± 1.24, p = 0.00005) (Fig. 3). Ht and HtSDS were positively correlated after treatment with the predicted Ht (PAH) before treatment (Fig. 4), and negatively correlated with the bone age/statural age ratio before treatment (p < 0.05) (Fig. 5). Before and after treatment PAH correlated inversely with the bone age/statural age ratio (p < 0.05) (Fig. 6, 7).

Two subgroups were analyzed, according to the patients’ age when GnRHa therapy was introduced. Group 1 consisted of girls under the age of 7 at the start of the therapy, and Group 2 included girls aged 7 and older. There was a statistically significant difference in the PAH SDS before treatment between these two subgroups: Group 1: (-) 1.3 ± 1.8 vs. Group 2: (-) 0.14 ± 1.2 (p < 0.05) and no significant difference in their PAH SDS after treatment: Group 1: (-) 0.7 ± 1.1 vs. Group 2: 0.31 ± 1.2. Thus, earlier introduction of GnRHa therapy, under the age of 7, results in a better height prognosis in girls with precocious puberty.

Fig. 1. Decline in height SDS (p = 0.0002)

Height SDS – height standard deviation score; SDS beginning – height standard deviation score at the beginning of GnRHa therapy; SDS end – height standard deviation score at the end of GnRHa therapy

Fig. 2. Deceleration of bone age (BA) in the first two years of GnRHa treatment (p = 0.0008)

BA diff. in the first year – deceleration of bone age in the first year of GnRHa treatment; BA diff. in second year – deceleration of bone age in the second year of GnRHa treatment
Discussion

GnRHa therapy has been applied as the treatment of choice in CPP for about 30 years. The main aim of GnRHa therapy is to preserve the patient’s height potential and to prevent psychosocial complications. The results of long-term studies concerning final auxological outcomes of this therapy have been the subject of numerous studies [3–5, 12–14]. The European Society for Pediatric Endocrinology (ESPE) has worked out a consensus concerning GnRHa therapy in children with CPP [15].

Factors influencing the final height outcomes in patients with CPP treated with GnRHa have

Fig. 4. Correlation between height SDS after treatment and predicted height (PAH) before treatment ($r = 0.69, p < 0.05$)

Fig. 5. Correlation between height SDS after treatment and bone age/statural age ratio before treatment ($r = -0.07, p < 0.05$)

Fig. 6. Correlation between PAH SDS before treatment and bone age/statural age ratio after treatment ($r = -0.57, p < 0.05$)

Fig. 7. Correlation between PAH SDS after treatment and bone age/statural age ratio after treatment ($r = -0.83, p < 0.05$)
been analyzed. The greatest height gain (defined as adult height minus predicted adult height at baseline) was noted in girls with puberty onset under the age of 6 (mean height gain 9–10 cm) [12]. Decisions concerning GnRHa therapy in girls with puberty onset at an older age should be individualized.

Some studies have shown that GnRHa therapy was effective in improving final height only in girls with CPP onset under the age of 6 [5, 15]. Lazar et al. concluded that height gain after treatment was higher in CPP girls who were treated being under the age of 6 [5]. The results of the present study are consistent with these observations: The CPP girls who started GnRH therapy under the age of 7 had a better height prognosis after GnRHa treatment. Chiavaroli et al. analyzed the effect of GnRHa therapy on adult height in girls with early puberty (onset between the ages of 8 to 10) and found that the treatment had no positive impact on the girls’ final height. Additionally, they noted that girls with early puberty have an increased risk of polycystic ovarian syndrome [16].

Moreover, a shorter interval between the onset of CPP and the initiation of GnRHa therapy has been shown to be an important factor in improving the effect of the therapy on final adult height [15, 17].

The initial prediction of adult height according to the Bayley-Pinneau method based on bone age enables CPP children with reduced growth potential who are at risk of short stature to be identified. These children benefit most from GnRHa therapy [18].

GnRHa treatment results in suppression of gonadotropin secretion, delaying the bone maturation and the growth rate, with an improvement in PAH. Children with more advanced bone age may present greater deceleration of osseous maturation and growth velocity [6, 13].

Lee et al. [12] investigated factors influencing adult height in girls with CPP who were treated with GnRH-A. They proved that the growth rate during treatment was positively correlated with the patient’s final height. The growth rate of their CPP patients was comparable to that of healthy prepubertal children at the same age (5–6 cm/year) during the first 72 weeks of therapy, and 4–4.5 cm/year from 72nd to the 192nd week of treatment. Girls with more advanced bone age (BA) over chronological age (CA) had a higher height gain over PAH during treatment. Because girls with more advanced BA have a lower PAH before GnRH therapy, slowing down bone maturation during treatment results in a better height gain than initially predicted. This, however, does not explain why these patients do not achieve their full potential adult height. Maintaining a growth rate comparable to that of prepubertal children leads to a better adult height outcome [12].

The growth velocity in some CPP patients decreases below the normal limit during GnRHa therapy. Weise et al. analyzed the influence of GnRHa treatment on the growth of 100 girls with CPP. They concluded that the impairment of growth resulted from the premature growth plate senescence under the influence of estrogens. BA is a marker for growth plate senescence. Growth velocity during GnRHa therapy was negatively correlated with BA advancement, the duration and stage of puberty and with serum estradiol concentration before treatment [19]. Similarly, in the current study Ht and HtSDS were negatively correlated after treatment with the difference between BA and statural age before treatment. The height prediction both before and after treatment was worse in girls with more advanced bone age.

According to Lee et al., subnormal growth velocity during GnRHa therapy may be associated with a decrease in growth hormone and IGF-1 secretion due to suppression of gonadal steroids. The addition of growth hormone to GnRH therapy may improve the adult height in these patients [20, 21].

Several studies have shown a relationship between GnRHa treatment duration and adult height. The optimal height prognosis was observed when GnRHa therapy was discontinued at a chronological age (CA) of about 11 years and bone age (BA) of about 12 years. However, the decision to end GnRHa therapy should be based on an analysis of all the variables, including CA, BA, the duration of the therapy, growth velocity and target height [12, 15, 22].

The study has shown that GnRHa treatment has beneficial effect on height potential in most patients, especially in younger ones and those with a rapid progression of CPP. The authors plan a follow-up study of this group of patients after GnRHa treatment in order to evaluate the long-term impact of the therapy on their final height and the course of puberty.

The authors concluded that the patient’s age at the beginning of GnRHa therapy is an important predictor of height prognosis. Beginning therapy under the age of 7 improves the predicted adult height (PAH) during treatment. Height prediction during the entire treatment period is worse in children with a more advanced bone age compared with their statural age at the onset of treatment.
References


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