CLINICAL STUDY

Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty

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Abstract

The aim of this retrospective study was to analyze the factors which affected the auxological response to GnRH agonist treatment and the final height (FH) outcome in 71 girls with idiopathic and truly precocious (onset before 8 years) central puberty (CTPP) who had been treated with the same therapy protocol (Decapeptyl Depot, 60 μg/kg i.m. every 28 days) for at least 2 years (since 7.0 ± 1.3 (s.d.) years of age) and followed until puberty was completed and FH was reached.

During the entire treatment period we observed: (a) a decrease of height standard deviation scores (SDS) (from 1.5 ± 1.7 to 0.9 ± 1.3 SDS, P < 0.01); (b) a striking deceleration of bone age (BA), revealed by the subnormal ΔBA:Δchronological age (CA) ratio (0.2 ± 0.1); (c) an increase of predicted adult height (from 155.6 ± 7.0 to 160.7 ± 6.7 cm, P < 0.0005). Treatment interruption was followed by an important catch-down growth, with an FH (158.4 ± 5.8 cm) lower (P < 0.025) than that predicted at the end of therapy. However, FH fell within the population norm and the target range in respectively 87.3 and 90% of the patients. The tallest FH was recorded in the patients who started therapy at less than 6 years of age and in those who discontinued treatment at a BA of 12.0–12.5 years. At stepwise regression analysis, FH in the whole study population was positively affected by the following independent factors: (a) height at the end of therapy (F = 45.45, P < 0.0001); (b) pretreatment height (F = 13.91, P < 0.0005); (c) treatment duration (F = 8.51, P < 0.005); (d) target height (TH) (F = 7.70, P < 0.01).

We conclude that: (i) most girls with idiopathic CTPP treated by GnRH agonists may achieve an adult height within the population norm and/or their target range; (ii) the height gain from therapy onset until FH attainment, however, is generally rather limited (on average 2.9 cm) and only few patients are able to reach their target percentile; (iii) the most favorable height prognosis with respect to TH is generally observed in the subjects with the tallest height at the end of treatment and the lowest BA2:CA2 ratio, due to the important deterioration of height prognosis which frequently follows therapy interruption; (iv) FH is also significantly conditioned by both TH and treatment duration; (v) in order to strengthen the weak therapeutic effect of GnRH agonists in CTPP this treatment should be started as early as possible and discontinued at a BA of 12.0–12.5 years.

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Introduction

Gonadotropin-releasing hormone (GnRH) agonists are known to provide an effective and safe treatment for truly precocious (onset before 8 years in girls or 9 years in boys) puberty of central origin (CTPP), having been demonstrated to suppress the clinical signs of sexual maturation (1–3) and to reduce the rate of epiphyseal maturation (4–6). Although such agonists have been used for several years and represent the treatment of choice for CTPP, much controversy still persists both about the optimal duration of this treatment and about the most appropriate timing for its withdrawal.

In the present study we retrospectively analyzed the factors which conditioned the auxological response to GnRH treatment and final height (FH) outcome in a homogeneous population of girls with idiopathic CTPP in order to clarify these controversial points.

Materials and methods

Subjects

We retrospectively reviewed the hospital records of 71 girls with idiopathic CTPP who: (a) had attended our Clinics during the last 10 years; (b) had been treated...
Table 1  Chronological age (CA), bone age (BA), BA:CA ratio, height (H), predicted height (PH) and difference between target height and PH (TH – PH) both at the start (1) and at the end (2) of the treatment period.

<table>
<thead>
<tr>
<th>Value</th>
<th>CA1 (years)</th>
<th>BA1 (years)</th>
<th>BA1:CA1 ratio</th>
<th>H1 (SDS)</th>
<th>PH1 (cm)</th>
<th>TH – PH1 (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At start</td>
<td>Mean ± S.D.</td>
<td>7.0 ± 1.3</td>
<td>9.8 ± 1.4</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 1.7</td>
<td>155.5 ± 7.0</td>
</tr>
<tr>
<td>Range</td>
<td>2.6–9.2</td>
<td>6.0–12.5</td>
<td>0.9–2.8</td>
<td>-2.8–3.8</td>
<td>-142.3–171.7</td>
<td>-9.5–24.7</td>
</tr>
<tr>
<td>At end</td>
<td>Mean ± S.D.</td>
<td>11.0 ± 1.0</td>
<td>12.4 ± 0.8</td>
<td>1.1 ± 0.1a</td>
<td>0.9 ± 1.3b</td>
<td>160.7 ± 6.7c</td>
</tr>
<tr>
<td>Range</td>
<td>8.6–12.6</td>
<td>10.0–14.0</td>
<td>0.8–1.3</td>
<td>-1.8–3.8</td>
<td>148.8–176.0</td>
<td>-14.5–18.6</td>
</tr>
</tbody>
</table>

*a P < 0.0001 vs BA1:CA1 ratio; b P < 0.01 vs H1; c P < 0.0005 vs PH1; d P < 0.0005 vs TH – PH1.

with the same therapy protocol (Decapeptyl Depot, o-Trp6-GnRH, IPSEN-Biotech, Milan, Italy, at a dose of 60 μg/kg i.m. every 28 days which was modified only in the case of inadequate gonadal suppression) since at least 9.2 years of age (mean 7.0 ± 1.3, range 2.6–9.2) and for at least 2 years (mean 3.9 ± 1.3, range 2.0–7.3): (c) had been followed after cessation of therapy until puberty was completed and FH was reached; (d) were not affected by dysmorphic syndromes, skeletal dysplasias, chronic diseases, or other associated conditions that could affect FH; (e) exhibited no morphological abnormalities on magnetic resonance imaging.

In all of the girls recruited for this study physical signs of puberty had appeared before the age of 8 years, together with an auxological course characterized by accelerated growth and bone maturation (Table 1); hormonal examinations revealed values within the pubertal range in all cases.

The average bone age (BA) at the start of therapy (BA1) was significantly advanced (P < 0.0001) with respect to chronological age (CA1), as also revealed by the increased BA1:CA1 ratio. Height was above the mean for CA in 58/71 cases. Pretreatment predicted height (PH1) was on average significantly lower than target height (TH) (P < 0.0005) and fell below TH in 52/71 individuals.

The main data of our patients both at the onset and at withdrawal of GnRH agonist treatment are scheduled in Table 1.

All the patients included in this study were divided into three groups according to their age at the start of GnRH agonist treatment: Group A (11 girls treated since less than 6 years of age: mean 4.6 ± 1.1, range 2.6–5.8); Group B (46 girls treated since 6–8 years of age: mean 7.3 ± 0.5); Group C (14 girls treated since 8.1–9.2 years: mean 8.4 ± 0.4).

**Methods**

Both patients’ and their parents’ heights were measured by Harpenden stadiometers. Patients’ height standard deviation score (SDS) at the onset (H1) and at the end (H2) of therapy were calculated according to the standards of Sempe et al. (7).

Previous radiographs of the hand and wrist were re-evaluated according to Greulich & Pyle (8). Adult height predictions both at the onset (PH1) and at the end of GnRH treatment (PH2) were performed by the method of Bayley & Pinneau (9), using the tables for accelerated girls when BA was advanced for CA by 1 year or more and using the tables for average girls when BA was within 1 year for CA.

TH was calculated from the measured parents’ height and determined by (father’s height + mother’s height + 13/2) (10).

FH was defined as a growth rate of less than 0.5 cm/year during the preceding year in girls with a BA greater than 15 years.

The short-term effectiveness of treatment was evaluated by the difference between PH2 and PH1, whereas the difference between FH and PH1 was used to assess long-term height gain. Residual growth capacity at the point of treatment discontinuation was measured by the difference between FH and H2.

The adequacy of gonadal suppression under therapy was evaluated both by serum levels of gonadotropins and estradio and by pelvic ultrasonography.

**Statistical analysis**

All results are expressed as mean ± s.d. Comparisons between H1, H2, PH1, PH2, FH and TH within the same patients were made by paired Student’s t-test. Student’s unpaired t-test was used to compared FH of the patients grouped according to CA at therapy onset or BA at therapy cessation. The Mann–Whitney U test was used to compare the non-parametric data. Differences in the proportion of patients with subnormal height prognosis at the start and at the end of therapy were compared by a chi-square test. To determine the effects of a number of auxological variables on either FH – PH1, or FH, or TH – FH, a stepwise multiple
regression analysis was carried out using either FH – PH1, or FH, or TH – FH as the dependent variable. The variables were: (a) FH – PH1 = CA, BA and BA:CA ratio both at the onset and the end of therapy and \( \Delta BA:CA \) ratio during the treatment period; (b) FH = CA, BA and BA:CA ratio both at the onset and at the end of therapy; \( \Delta BA:CA \) ratio during treatment period; treatment duration; H1 and H2; (c) TH – FH = CA, BA and BA:CA ratio both at the onset and at the end of therapy; \( \Delta BA:CA \) ratio during the treatment period; treatment duration; H1 and H2.

In all the tests P values <0.05 were considered to reflect statistical significance.

Results

Auxological evaluation from the start to the end of therapy

The main auxological data of the 71 patients both at the start and at the end of therapy are summarized in Table 1.

A significant growth deceleration occurred during the entire treatment period, as revealed by the decrease of height SDS from the start to the end of therapy (\( P < 0.01 \)). Growth deceleration was accompanied by a striking deceleration of bone maturation, as demonstrated by the subnormal \( \Delta BA:CA \) ratio recorded in this period (0.2 ± 0.1). Thanks to the significant decrease of BA:CA ratio observed during the treatment period (\( P < 0.0001 \)), PH increased dramatically from the start to the cessation of therapy (\( P < 0.0005 \)), with an average difference of 5.2 ± 5.9 cm between PH2 and PH1. PH at discontinuation of treatment was very close to TH (Table 1).

Final evaluation

The residual growth capacity at the point of therapy discontinuation, as expressed by the height increment which followed the end of therapy (FH–H2), was only 8.7 ± 4.9 cm. Consequently treatment interruption was followed by an important catch-down growth, with an FH SDS significantly lower with respect to H2 SDS (–0.4 ± 1.0 vs 0.9 ± 1.3 SDS, \( P < 0.0001 \)). Due to it, a significant deterioration of height prognosis was observed after therapy withdrawal: FH was on average 2.9 ± 6.0 cm greater than PH1 (\( P < 0.01 \)), but 2.3 ± 3.3 and 3.1 ± 6.0 cm lower than respectively PH2 (\( P < 0.025 \)) and TH (\( P < 0.005 \)), falling approximately midway between PH1 and both PH2 and TH (Table 2).

However, only 12.7% of patients achieved a subnormal FH (<–2.0 SDS) whereas the prevalence of girls with subnormal PH1 (35.2%) was significantly higher (\( \chi^2 = 9.90, P < 0.005 \)). Moreover the percentage of girls with FH below the lower limit of target range was significantly less if compared with the one predicted at the onset of treatment (10 vs 35.2%; \( \chi^2 = 13.07, P < 0.001 \)).

When the overall study population was divided into three subsets according to the age at therapy onset, FH significantly and progressively decreased from Group A to Group C. The best results in terms of FH were recorded in the patients treated since less than 6 years of age, who exhibited both an important improvement of height prognosis after the start of therapy and no deterioration of height prognosis after its interruption (Table 2). Nevertheless, due to their higher TH, Group A patients did not achieve an FH very close to TH and the difference between TH and FH in this group was similar to the one found in the girls of Groups B and C (Table 2).

Factors influencing height gain from therapy onset until FH attainment

Stepwise regression analysis revealed that only one variable, the BA1:CA1 ratio, was able to independently and positively influence the effective height gain from the start of treatment until the achievement of adult height (FH – PH1) when the other variables were excluded (F = 38.24, \( P = 0.0001 \)).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Final height (FH), target height (TH), difference between them (TH – FH), difference between FH and height predicted at the start (FH – PH1) and at the end of therapy (FH – PH2) in the entire series and in three subsets of patients with different ages at therapy onset; in brackets the number of cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire series (n = 71)</td>
<td>FH (cm)</td>
</tr>
<tr>
<td>Range</td>
<td>144.0–172.0</td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>158.4 ± 5.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group A (n = 11) Mean ± s.d.</td>
<td>160.9 ± 5.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group B (n = 46) Mean ± s.d.</td>
<td>158.4 ± 5.8&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group C (n = 14) Mean ± s.d.</td>
<td>156.2 ± 5.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> \( P < 0.0005 \) vs TH; <sup>b</sup> \( P < 0.0005 \) vs Group C; <sup>c</sup> \( P < 0.0025 \) vs Group C; <sup>d</sup> \( P < 0.05 \) vs Group B; <sup>e</sup> \( P < 0.0005 \) vs Groups B and C.
Factors influencing FH

If the entire study population was divided into four different groups according to BA2, the tallest adult height was achieved by the patients who discontinued treatment at a BA of 12.0–12.5 years, whilst the worst auxological outcome was observed in those who stopped therapy at a BA exceeding 13 years: Group A (11 patients who discontinued therapy at a BA ranging from 10.0 to 11.9 years) FH = –0.5 ± 1.0 SDS; Group B (33 subjects who stopped therapy at a BA of 12.0–12.5 years) FH = –0.31.0 SDS; Group C (14 patients who discontinued treatment at BA ranging from 12.6 to 13.0 years) FH = –0.8 ± 1.0 SDS; Group D (12 subjects who discontinued treatment at a BA of 13.1–14.5 years) FH = –1.3 ± 1.1 SDS, P < 0.005 vs Group B.

At stepwise regression analysis four variables were found to independently (and positively) influence FH to a significant degree: (a) H2 (F = 45.45, P < 0.0001); (b) H1 (F = 13.94, P < 0.0005); (c) treatment duration (F = 8.51, P < 0.005); (d) TH (F = 7.70, P < 0.01).

The difference between TH and FH was either negatively or positively influenced by respectively BA2:CA2 ratio (F = 6.54, P < 0.02) or H2 (F = 6.32, P < 0.02).

Discussion

Based on a large and homogeneous series of girls with idiopathic CTPP treated for at least 2 years with the same therapeutic protocol, the present study confirms that GnRH agonist treatment is frequently able to improve the auxological outcome of girls with CTPP. Moreover, our data shed further light on the factors which can affect the long-term auxological response to this treatment in CTPP.

Since one of the main purposes of the therapy with GnRH agonists in CTPP is to allow the achievement of an FH within both target range and the population norm, we can conclude that this treatment was successful in most patients of our series. The ultimate height of our patients, in fact, exceeded the upper limit of the target range in 5.6% of cases and fell within target range in 76.1% of subjects and within the population norm in 87.4% of cases. Moreover it resulted in an average not far from the mean TH.

The mean FH of our patients compared favorably (4, 5, 11, 12) or unfavorably (13–16) with the one reported by other authors in CTPP girls treated with GnRH agonists.

At stepwise regression analysis, FH in our study populations was significantly and positively affected by the following independent factors, in increasing order of relevance: treatment duration, TH, H1 and H2. Each of these factors was able to influence the statural outcome of our patients even when the other variables were excluded from the analysis.

The positive influence of treatment duration on FH is probably to be interpreted in the light of the negative relationship between CA1 and FH found by others in CTPP (15); the earlier the treatment onset and the longer the treatment duration, the greater the FH. It is to be underlined that the tallest FH in our series was attained by the girls who started therapy before 6 years of age.

FH in our patients was also significantly conditioned by TH, which suggests that the genetic influences on growth are conserved in CTPP, at least when GnRH agonists are administered. A similar conclusion had already been reported by other authors (15, 16).

H1 was another positive factor contributing to FH, although the relevance of this factor in our series was clearly less than in the report by Oostdijk et al. (16).

The most important factor positively influencing FH outcome in our patients was H2, a finding which demonstrates that the improvement in CTPP can be obtained only before treatment with GnRH agonists is withdrawn. This statement is further supported by the important catch-down growth and height prognosis deterioration which followed therapy discontinuation in our patients. Their FH, in fact, was on average 2.8 cm higher with respect to PH1, but 1.8 cm lower than PH2; consequently almost half of the gain in PH during treatment was lost between the time therapy was stopped and the time adult height was reached. A similar trend has been described by other authors (11, 16–19) and is probably due to the significant increase of ΔBA:ΔCA ratio which has been reported to follow therapy cessation (16, 19).

As far as the optimal timing for discontinuing treatment is concerned, the best statural outcome in our series was achieved by the patients who stopped treatment at a BA ranging from 12.0 to 12.5 years, whose FH was significantly greater than that recorded in the girls who stopped treatment too late (after a BA of 13.0). These data do not differ from those reported by other authors (16) and substantiate the view that GnRH therapy discontinuation in girls with CTPP should be taken into consideration at a BA of 12.0–12.5 years. According to other studies the optimal timing for withdrawing treatment would be 11.5 years (12, 20).

The positive change in predicted stature observed in our patients from the start of therapy until the achievement of adult height was similar to the one recorded by other authors (5, 16, 19, 21) in girls treated with s.c. or i.m. GnRH preparations (from 2.4 to 3.5 cm). The most remarkable positive change from PH1 to FH (10.0 cm) has been reported in a series of CTPP girls treated since less than 5 years of age, with an average difference of 6 cm between patients treated either before or after 5 years old (15). Such a report suggested that the salutary effects of GnRH agonist therapy on FH are more clear-cut in the younger-treated patients. In our study population the difference
between FH and PH1 was more evident in the subset of girls treated since less than 6 years old, which confirms that an early start of treatment in girls with CTPP may have a favorable impact on their ultimate height gain.

The positive difference between FH and PH1 in our series was significantly influenced only by the BA:CA ratio at the point of treatment starting, a finding which confirms that the therapeutic effects of GnRH agonists (if evaluated by the difference between FH and PH1) are apparently best in the girls with the most advanced BA at the onset of treatment (14), due to the most compromised PH1. On the contrary, the therapeutic effects of GnRH agonists (if evaluated only on the basis of FH outcome) may be negatively conditioned by an excessive BA advancement at the onset of therapy (15, 21).

Conclusions

Most girls with idiopathic CTPP treated by GnRH agonists may achieve an adult height within the population norm and/or their target range.

The height gain from therapy onset until FH attainment, however, is generally rather limited (on average 2.9 cm) and only few patients are able to reach their target percentile.

The most favorable height prognosis with respect to TH is generally observed in the subjects with the tallest H2 and the lowest BA2:CA2 ratio, due to the important deterioration of height prognosis which frequently follows therapy interruption.

FH is also significantly influenced by both TH and treatment duration.

In order to strengthen the weak therapeutic effect of GnRH agonists in CTPP this treatment should be started as early as possible and discontinued at a BA of 12.0–12.5 years.

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