Adult Height in Girls with Central Precocious Puberty Treated with Gonadotropin-Releasing Hormone Analogues and Growth Hormone

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ABSTRACT

GnRH analogues (GnRHa) represent the treatment of choice in central precocious puberty (CPP), because arresting pubertal development and reducing either growth velocity (GV) or bone maturation (BA) should improve adult height. However, in some patients, GV decrease is so remarkable that it impairs predicted adult height (PAH); and therefore, the addition of GH is suggested. Out of twenty subjects with idiopathic CPP (treated with GnRHa depot-triptorelin, at a dose of 100 µg/kg im every 21 days, for at least 2–3 yr), whose GV fall below the 25th percentile for chronological age, 10 received, in addition to GnRHa, GH at a dose of 0.3 mg/kg/week sc, 6 days weekly, for 2–4 yr; and 10 matched for BA, chronological age, and duration of GnRHa treatment, who showed the same growth pattern but refused GH treatment, served to evaluate the efficacy of GH addition. No patient showed classical GH deficiency. Both groups discontinued treatment at a comparable BA (mean ± SEM): 13.2 ± 0.2 in GnRHa plus GH vs. 13.0 ± 0.1 yr in the control group. At the conclusion of the study, all the patients had achieved adult height. Adult height was considered to be attained when the growth during the preceding year was less than 1 cm, with a BA of over 15 yr. Patients of the group treated with GH plus GnRHa showed an adult height significantly higher (P < 0.001) than pretreatment PAH (160.6 ± 1.3 vs. 152.7 ± 1.7 cm). Target height (TH) was significantly exceeded. The group treated with GnRH alone reached an adult height not significantly higher than pretreatment PAH (157.1 ± 2.5 vs. 155.5 ± 1.9 cm). TH was just reached but not significantly exceeded. The gain in centimeters obtained, calculated between pretreatment PAH and final height, was 7.9 ± 1.1 cm in patients treated with GH combined with GnRHa; whereas in patients treated with GnRHa alone, the gain was just 1.6 ± 1.2 cm (P = 0.001). Furthermore, no side effects have been observed either on bone age progression or ovarian cyst appearance and the gynecological follow-up in the GH-treated patients (in comparison with those treated with GnRHa alone). In conclusion, a gain of 7.9 cm in adult height represents a significant improvement, which justifies the addition of GH for 2–3 yr during the conventional treatment with GnRHa, especially in patients with CPP, and a decrease in GV so marked as to impair PAH, not allowing it to reach even the third centile. (J Clin Endocrinol Metab 84: 449–452, 1999)
TABLE 1. Auxological data of 10 CPP patients treated with GnRHa plus GH

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>At start of GnRHa</th>
<th>At start of GnRHa+GH</th>
<th>At end of GnRHa+GH</th>
<th>At adult height</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (yr)</td>
<td>6.3 ± 0.4</td>
<td>7.9 ± 0.6</td>
<td>10.0 ± 0.5</td>
<td>13.0 ± 0.5</td>
<td>14.6 ± 0.6</td>
</tr>
<tr>
<td>BA (yr)</td>
<td>9.1 ± 0.5</td>
<td>10.6 ± 0.4</td>
<td>12.0 ± 0.2</td>
<td>13.2 ± 0.2</td>
<td>15.6 ± 0.4</td>
</tr>
<tr>
<td>Height (SDS score for BA)</td>
<td>−1.2 ± 0.2</td>
<td>−1.5 ± 0.2</td>
<td>−1.2 ± 0.2</td>
<td>+0.22 ± 0.2</td>
<td>16.0 ± 1.3</td>
</tr>
<tr>
<td>PAH (cm)</td>
<td>156.0 ± 1.5</td>
<td>152.7 ± 1.7</td>
<td>153.5 ± 1.7</td>
<td>163.2 ± 1.7</td>
<td>160.6 ± 1.3</td>
</tr>
<tr>
<td>Target height (cm)</td>
<td>155.6 ± 2.0a</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are the mean ± SEM.

a P < 0.001 vs. start of GnRHa.

b P < 0.05 vs. adult height.

TABLE 2. Auxological data of 10 CPP patients treated with GnRHa alone

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>At start of GnRHa</th>
<th>At end of GnRHa</th>
<th>At adult height</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (yr)</td>
<td>5.7 ± 0.6</td>
<td>7.6 ± 0.2</td>
<td>12.5 ± 0.4</td>
<td>14.3 ± 0.4</td>
</tr>
<tr>
<td>BA (yr)</td>
<td>7.9 ± 1.1</td>
<td>10.4 ± 0.3</td>
<td>13.0 ± 0.1</td>
<td>15.5 ± 0.3</td>
</tr>
<tr>
<td>Height (SDS score for BA)</td>
<td>−1.3 ± 0.9</td>
<td>−1.0 ± 0.3</td>
<td>−0.4 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>PAH (cm)</td>
<td>157.5 ± 2.9</td>
<td>155.5 ± 2.0</td>
<td>159.6 ± 2.3</td>
<td>157.1 ± 2.5</td>
</tr>
<tr>
<td>Target height (cm)</td>
<td>155.5 ± 2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are the mean ± SEM.

a P < 0.01 vs. start of GnRHa.

GnRHa. Screening blood tests (to assess metabolic, hepatic, renal, hematological, and thyroid function) were also performed at each evaluation. In addition, an oral glucose tolerance test was performed every 12 months in the patients receiving GnRHa+GH treatment. Pelvic ultrasonography, to evaluate uterine and ovarian volumes, was performed every 6 months. Midparental TH was calculated from the mean height of the parents, adjusted for sex, as described by Tanner et al. (27).

Both groups discontinued treatment at a comparable bone age and CA; BA (mean ± SEM), 13.2 ± 0.2 in GnRHa plus GH vs. 13.0 ± 0.1 yr in the GnRHa-alone group; and CA (mean ± SEM), 13 ± 0.4 vs. 12.5 ± 0.4 yr. At present, all the patients of this study achieved adult height. Adult height was considered to be attained when the growth during the preceding year was less than 1 cm, with a BA of over 15 yr.

GH was discontinued contemporaneously with GnRHa, regardless of the current criteria of withdrawal (i.e. GV less than 2 cm/yr and BA ≥ 14 yr).

Hormone assay

Plasma LH and FSH were measured in duplicate by immunoradiometric assay (Maiacron, Serono Biodata, Milan, Italy); estradiol was measured by RIA (DPC, Los Angeles, CA; Bio-Rad, Hercules, CA); GH was measured in duplicate by polyclonal RIA (Sorin Biomedica, Vercelli, Italy).

Statistical analysis

Data are expressed as mean ± SEM unless otherwise stated. Statistical analysis was performed by the paired and unpaired Student’s t test and ANOVA. A P value < 0.05 was considered significant.

Results

No side effects or changes in suppression of the hypothalamic-pituitary-gonadal axis were observed during the combined GnRHa+GH treatment. Plasma FSH and LH peaks after the LHRH test were suppressed during treatment, significantly lower than pretreatment, both in the GnRHa+GH-treated group (peak LH: 0.61 ± 0.17 vs. 26.7 ± 2.8 IU/L, peak FSH: 14.0 ± 0.08 vs. 12.5 ± 0.86 IU/L, both P < 0.05) and in the GnRHa-alone-treated group (peak LH: 0.76 ± 0.17 vs. 26.7 ± 5.5 IU/L, peak FSH: 1.0 ± 0.2 vs. 17.0 ± 2.5 IU/L, both P < 0.05). After the withdrawal of treatment, peak LH rose back to 14.22 ± 5.7 and FSH peak to 10.58 ± 2.17 IU/L within 1 yr in the combined group; and peak LH arose to 11.87 ± 2.9 and FSH peak 9.13 ± 0.92 IU/L within a similar period in the GnRHa-alone-treated group (P < 0.05).

We did not observe abnormal advancement in bone age or untoward side effects in the GH-treated group; BA progressed with the same velocity until epiphyseal closure after discontinuation of treatment without any significant difference between the two groups.

On treatment, pelvic ultrasound showed reduced ovarian volume in both groups; and ovarian cyst appearance, previously described by some authors (28), was not observed in GH-treated girls. Ovarian volumes were reduced from 3.08 ± 0.36 to 1.78 ± 0.19 during treatment, increased to 5.66 ± 0.24 cm3 (P < 0.05) after 1 yr off therapy in the GnRHa+GH-treated group. Similarly, in the GnRHa-alone-treated group, ovarian volumes during therapy reduced from 2.33 ± 0.36 to 1.59 ± 0.12 and increased to 4.64 ± 0.48 cm3 (P < 0.05) after 1 yr without therapy, showing a similar increment. No significant difference was found between ovarian volumes of both groups at 1 yr without treatment. The uterine length remained unchanged during treatment (from 4.7 ± 0.39 to 4.5 ± 0.2 cm) and increased to 6.3 ± 0.29 cm (P < 0.05) after 1 yr off therapy in the GnRHa+GH-treated group. Similarly, in the GnRHa-alone-treated group, uterine length remained unchanged during therapy (from 4.2 ± 0.22 to 4.2 ± 0.13 cm) and increased to 5.72 ± 0.29 cm (P < 0.05) after 1 yr without therapy, showing a comparable increment.

In both groups, menarche occurred in coincidence with the resumption of FSH and LH secretion; and increments of ovarian volumes and uterine length occurred about 8–18 months (average 1 yr) after the discontinuation of therapy. Subsequent menses were regular, without any difference between the two groups, at least at present, after a further year of observation.

As for group 1, PAH at the start of GnRHa-alone treatment (152.7 ± 1.7 cm) was not significantly different from PAH at the start of GnRHa+GH treatment (153.5 ± 1.7 cm), and it increased significantly to 163.2 ± 1.7 cm at the end of com-
bined therapy ($P < 0.001$). Adult height was $160.6 \pm 1.3$ cm, remaining significantly higher ($P < 0.001$) than pretreatment PAH and not significantly lower ($P = $not significant) than PAH at the end of treatment. TH was significantly exceeded ($P < 0.05$) (Table 1).

As for group 2, PAH at the start of GnRHa alone was $155.5 \pm 2.0$ and increased to $159.6 \pm 2.3$ cm at the end of treatment [still significantly, but to a lesser extent than in group 1 ($P < 0.01$)]. Adult height in these patients was not significantly higher than pretreatment PAH ($157.1 \pm 2.5$ vs. $155.5 \pm 1.9$) cm. TH was reached but not exceeded ($P =$ not significant) (Table 2).

### Discussion

Idiopathic CPP includes a heterogeneous group of patients differing in age, bone age, genetic factors determining height, and associated conditions. Perhaps for these reasons, a subset of these patients shows a worse response to GnRHa. Beside a variable implication of GH secretion, which is not classically deficient in some patients like ours, the addition of growth hormone to GnRHa has been suggested by some authors, for these patients and even for short normal subjects with early or normal puberty (29, 30). Because, in our patients, GH was not classically deficient, we used a dose higher than the replacement GH dose, on the basis of the same rationale used in short normal children (31, 32).

The gain in centimeters obtained in our study, calculated between pretreatment PAH ($152.7 \pm 1.7$) and final height ($160.6 \pm 1.3$ cm), was $7.9$ cm $\pm 1.1$ in patients treated with GH+GnRHa, whereas in patients treated with GnRHa alone, the gain between pretreatment PAH ($155.5 \pm 1.7$) and final height ($157.1 \pm 2.5$ cm) was just $1.6$ cm $\pm 1.2$. The difference of the gain obtained in the groups is significant, in favor of group 1 ($P = 0.001$).

Thus, final results of our experience show that the gain calculated just on PAH decreased when adult height was attained and compared with pretreatment PAH in both groups. In the same patients, we previously reported results at 3 yr (20), showing a mean gain of $13.5$ cm in PAH in the GH+GnRHa group, which became $7.9$ cm as adult height; and of $6$ cm in the GnRHa-alone group, which became $1.6$ cm as adult height. This could be caused by the limits of height prediction methods, based on bone ages at the beginning, accelerated by precocious puberty, and afterward decelerated by treatment (9). Another reason of loss in centimeters, in group 1, could be our protocol design, which stipulated discontinuation of GH contemporaneously with GnRHa, regardless of current criteria for GH discontinuation (i.e. GV less than 2 cm/yr and bone age $\geq$ 14 yr).

However, a gain of $7.9$ cm in adult height represents a significant improvement, which justifies the addition of GH for 2–3 yr during the conventional treatment with GnRHa, especially in patients with CPP and a decrease in GV, so marked as to impair PAH, not allowed to reach even the third centile.

Furthermore, no adverse effects, either on bone age or on ovarian morphology and function, have been observed. Bone age progressed at the same rate in both groups, and menarche occurred about 1 yr after discontinuation of treatment. Subsequent menses were regular, and no ovarian cysts appeared, so far. In conclusion, TH was significantly exceeded by patients treated with combined therapy.

Based on our data, the most propitious strategy for optimal treatment (especially in girls with CPP with a very short PAH) can be to prolong the GH administration after GnRHa discontinuation, until the closure of epiphyses, to sustain growth during the residual pubertal spurt, as suggested in a study on short normal girls treated with GH+GnRHa (29).

### References

gonadotropin-releasing hormone analog and growth hormone in central pre-cocious puberty. J Clin Endocrinol Metab. 81:948–951.


