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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)

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 (1–9). However, in some patients, GV decrease is so remarkable that predicted adult height (PAH) is impaired (10, 11); and therefore, some investigators suggest, on the basis of several (though controversial) studies on GH secretion in this subset of CPP patients (12–16), the combination of GnRHa with GH (17–21).

We report here the adult height of a group of 10 girls with idiopathic CPP treated with combined therapy, compared with that of 10 CPP girls matched for auxological data, duration of treatment, and severe growth deceleration treated with GnRHa alone.

Subjects and Methods

Subjects

Ten girls with idiopathic CPP, diagnosed according to the classic criteria (22), whose GV during GnRHa treatment (depot-Triptorelin, 100 g/kg every 21 days im) decreased below the 25th centile for chronological age (CA), with no improvement in PAH, received GH at a dose of 0.3 mg/kg·week sc 6 days weekly for 3.07 ± 1.33 yr (Group 1). Auxological data at diagnosis, at the start of GnRHa therapy, at the start of GnRHa+GH therapy, and at the end of treatment and adult height are shown in Table 1. The GV decrease (from 8.3 ± 0.8 to 3.8 ± 0.4 cm/yr) was observed after 2–3 yr of GnRHa treatment, and GH was given at the third year.

Ten girls with idiopathic CPP (matched for BA, CA, and duration of GnRHa treatment), who showed a similar deceleration of growth (below the 25th centile for CA) at comparable times, did not receive GH treatment; and their data were used in comparison to better evaluate the efficacy of GH addition (Group 2). Their auxological data are shown in Table 2.

All patients were euthyroid; GH secretory status has been studied at the time of growth deceleration. Twelve patients underwent GH stimulation tests (arginine, L-dopa) and showed a normal GH response, with a peak more than 10 g/L; in the remaining eight patients, evaluation of spontaneous GH secretion was performed by measuring GH in blood sampled every 20 min from 2000 h to 0800 h: the mean value (mean ± SD) was 5.8 ± 3.0 μg/L (normal, >3.6 μg/L).

The study was approved by the Ethical Committee of our institution; written consent was obtained from parents of children who received GH. Both groups of patients were evaluated at the start of treatment and every 6 months, either during the course of treatment or after the withdrawal. At each evaluation, height was measured three times with a Harpenden stadiometer. Bone age was determined according to the method of Greulich and Pyle (23) by the same observer, and adult height was predicted according to the Bayley and Pinneau method (24). Pubertal staging was evaluated using the method of Tanner (25, 26). Plasma samples, for determination of sex steroid levels, were obtained every 6 months; and gonadotropins were evaluated every 6 months after the iv administration of 100 μg of LH-releasing hormone (LHRH) (sampling at 15 and 0 min before and 15, 30, 60, 90, and 120 min after LHRH); the LHRH stimulation test was performed on day 20 after injection of the

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TABLE 1. Auxological data of 10 CPP patients treated with GnRHa plus GH

	At diagnosis	At start of GnRHa	At start of GnRHa+GH	At end of GnRHa+GH	At adult height
CA (yr)	6.3 ± 0.4	7.9 ± 0.6	10.0 ± 0.5	13.0 ± 0.5	14.6 ± 0.6
BA (yr)	9.1 ± 0.5	10.6 ± 0.4	12.0 ± 0.2	13.2 ± 0.2	15.6 ± 0.4
Height (SDS score for BA)	−1.2 ± 0.2	−1.5 ± 0.2	−1.2 ± 0.2	+0.22 ± 0.2[a]	
PAH (cm)	156.0 ± 1.5	152.7 ± 1.7	153.5 ± 1.7	163.2 ± 1.7[a]	160.6 ± 1.3[a]
Target height (cm)	155.6 ± 2.0[b]				

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

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

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 ultrasound, 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 immmunoradiometric assay (Maiaclone, Serono Biodata, Milan, Italy); estradiol was measured by RIA (DPC, Los Angeles, CA; Bio-Rad, Hercules, CA); GH was measured in duplicate by policlonal 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: 1.4 ± 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 ± 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 ± 2.0 and increased to 159.6 ± 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 ± 2.5 *vs.* 155.5 ± 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 ± 1.7) and final height (160.6 ± 1.3 cm), was 7.9 cm ± 1.1 in patients treated with GH+GnRHa, whereas in patients treated with GnRHa alone, the gain between pretreatment PAH (155.5 ± 1.7) and final height (157.1 ± 2.5 cm) was just 1.6 cm ± 1.2. The difference between 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 ≥ 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

1. **Oerter KE, Manasco P, Barnes KM, Jones J, Hill S, Cutler GB.** 1991 Adult height in precocious puberty after long-term treatment with deslorelin. J Clin Endocrinol Metab. 73:1235–1240.
2. **Antoniazzi F, Cisternino M, Nizzoli G, et al.** 1994 Final height in girls with central precocious puberty: comparison of two different luteinizing hormone-releasing hormone agonist treatments. Acta Paediatr. 83:1052–1056.
3. **Brauner R, Adan L, Malandry F, Zantleifer D.** 1994 Adult height in girls with idiopathic true precocious puberty. J Clin Endocrinol Metab. 79:415–420.
4. **Cacciari E, Cassio A, Balsamo A, et al.** 1994 Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. Arch Pediatr Adolesc Med. 148:1194–1199.
5. **Kletter GB, Kelch RP.** 1994 Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty. J Clin Endocrinol Metab. 79:331–334.
6. **Stasiowska B, Vannelli S, Benso L.** 1994 Final height in sexually precocious girls after therapy with an intranasal analogue of gonadotrophin-releasing hormone (Buserelin). Horm Res. 42:81–85.
7. **Paul D, Conte FA, Grumbach MM, Kaplan SL.** 1995 Long-term effect of gonadotropin-releasing hormone agonist therapy on final and near-final height in 26 children with true precocious puberty treated at a median age of less than 5 years. J Clin Endocrinol Metab. 80:546–551.
8. **Oostdijk W, Rikken B, Schreuder S, et al.** 1996 Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. Arch Dis Child. 75:292–297.
9. **Kauli R, Galatzer A, Kornreich L, et al.** 1997 Final height of girls with central precocious puberty, untreated *versus* treated with cyproterone acetate or GnRH analogue. Horm Res. 47:54–61.
10. **Oostdijk W, Drop SLS, Odink RJH, Hummelink R, Partsch CJ, Sipell WG.** 1991 Long-term results with a slow-release gonadotrophin-release hormone agonist in central precocious puberty. Acta Paediatr. [Suppl] 372:39–45.
11. **Saggese G, Bertelloni S, Baroncelli GI, Di Nero G, Battini R.** 1993 Growth velocity and serum aminoterminal propeptide of type III procollagen in precocious puberty during gonadotropin-releasing hormone analogue treatment. Acta Paediatr. 82:261–266.
12. **Stanhope R, Pringle PJ, Brook CGD.** 1988 Growth, growth hormone and sex steroid secretion in girls with central precocious puberty treated with a gonadotrophin releasing hormone (GnRH) analogue. Acta Paediatr. 77:525–530.
13. **Di Martino-Nardi J, Wu R, Fishman K, Saenger P.** 1991 The effect of long-acting analog of luteinizing hormone-releasing hormone on growth hormone secretory dynamics in children with precocious puberty. J Clin Endocrinol Metab. 73:902–906.
14. **Di Martino-Nardi J, Wu R, Varner R, Wong WLT, Saenger P.** 1994 The effect of luteinizing hormone-releasing hormone analog for central precocious puberty on growth hormone (GH) and GH-binding protein. J Clin Endocrinol Metab. 78:664–668.
15. **Sklar CA, Rothenberg S, Blumberg D, Oberfield SE, Levine LS, David R.** 1991 Suppression of the pituitary-gonadal axis in children with central precocious puberty: effects on growth, growth hormone, insulin-like growth factor-I, and prolactin secretion. J Clin Endocrinol Metab. 73:734–738.
16. **Kamp GA, Manasco PK, Barnes KM, et al.** 1991 Low growth hormone levels are related to increased body mass index and do not reflect impaired growth in luteinizing hormone-releasing hormone agonist-treated children with precocious puberty. J Clin Endocrinol Metab. 72:301–307.
17. **Saggese G, Pasquino AM, Bertelloni S, et al.** 1995 Effect of combined treatment with gonadotropin releasing hormone analogue and growth hormone in patients with central precocious puberty who had subnormal growth velocity and impaired height prognosis. Acta Paediatr. 84:299–304.
18. **Bridges NA, Brook CGD.** 1991 The growth of children with precocious puberty treated with a combination of LHRH analogue and growth hormone. Horm Res. [Suppl 2] 35:40.
19. **Partsch CJ, Oostdijk W, Albers N, et al.** 1995 Combined treatment with a depot GnRH agonist and GH in girls with central precocious puberty (CPP) and low height velocity: effects on growth and bone maturation. Horm Res. [Suppl 2]44:145.
20. **Pasquino AM, Municchi G, Pucarelli I, et al.** 1996 Combined treatment with

gonadotropin-releasing hormone analog and growth hormone in central precocious puberty. J Clin Endocrinol Metab. 81:948–951.
21. **Tatò L, Saggese G, Cavallo L, et al.** 1995 Use of combined Gn-RH agonist and hGH therapy for better attaining the goals in precocious puberty treatment. Horm Res. [Suppl 3] 44:49–54.
22. **Kaplan SL, Grumbach MM.** 1990 Pathophysiology and treatment of sexual precocity. J Clin Endocrinol Metab. 71:785–789.
23. **Greulich WW, Pyle SI.** 1959 Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press.
24. **Bayley N, Pinneau SR.** 1952 Tables for predicting adult height from skeletal age: revised for use with the Greulich and Pyle hand standards. J Pediatr. 40:423–441.
25. **Marshall WA, Tanner JM.** 1969 Variations in pattern of pubertal changes in girls. Arch Dis Child. 44:291–303.
26. **Marshall WA, Tanner JM.** 1970 Variations in pattern of pubertal changes in boys. Arch Dis Child. 45:13–23.
27. **Tanner JM, Goldstein H, Whitehouse RH.** 1970 Standards for children's height at ages 2–9 allowing for height of parents. Arch Dis Child. 45:755–762.
28. **Bridges NA, Cooke A, Healy MJR, Hindmarsh PC, Brook CGD.** 1995 Ovaries in sexual precocity. Clin Endocrinol (Oxf). 42:135–140.
29. **Saggese G, Cesaretti G, Barsanti S, Rossi A.** 1995 Combination treatment with growth hormone and gonadotropin-releasing hormone analogs in short normal girls. J Pediatr. 126:468–473.
30. **Balducci R, Toscano V, Mangiantini A, et al.** 1995 Adult height in short normal adolescent girls treated with gonadotropin-releasing hormone analog and growth hormone. J Clin Endocrinol Metab. 80:3596–3600.
31. **Hopwood NJ, Hintz RL, Gertner JM, et al.** 1993 Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. J Pediatr. 123:215–222.
32. **Buchlis JG, Irizarry L, Crotzer BC, et al.** 1998 Comparison of final heights of growth hormone-treated *vs.* untreated children with idiopathic growth failure. J Clin Endocrinol Metab. 83:1075–1079.