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The Effect of Pubertal Delay by GnRH Agonist in GH-Deficient Children on Final Height

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Several strategies can be applied to optimize GH treatment in GH-deficient (GHD) children during puberty (1). In a recent issue of *JCEM*, Mericq *et al.* (2) reported their results of a prospective, randomized trial on the effect of GH alone or in combination with GnRH agonist (GnRHa) in pubertal GHD patients. They concluded that delaying puberty by GnRHa led to a near final height (FH) SD score of -1.3 ± 0.5 compared with -2.7 ± 0.3 in the group treated with GH alone. However, in this study, the patients had been untreated up to the age of 12–18.5 yr, which is unusual for western countries. In addition, in several cases the growth retardation was less severe than would be expected in classical GHD patients without treatment.

Although a randomized controlled trial in a large and representative sample is certainly the best design to study the efficacy of a therapeutical regimen, a patient series with matched controls is a good second. We report on a retrospective analysis of the effect of the addition of GnRHa (shortly after the onset of puberty) to GH treatment in GHD children. Matched controls with GH treatment were used for comparison. The children were younger as well as shorter for age compared with the subjects in the randomized trial (2).

Patients and Methods

We selected from the nationwide database (n = 762) of GH-treated children (Dutch Growth Foundation/Advisory Group on Growth Hormone) 21 GHD patients who had reached FH and had been treated with the combination of GH and GnRHa (Triptorelin or Leuprolide acetate, 3.75 mg per month), after a variable period of GH therapy alone. GnRHa was given soon after entering into puberty at a relatively early age and/or low height for age.

Thereafter the database was screened for matched controls who were treated with GH only. Matching criteria included sex and height SD score at the start of puberty. These parameters were chosen to minimize probable confounding effects of differences in age and height SD score at the start of puberty between males and females. For 8 patients on the combination therapy (group A) suitable matched controls were found (group B). For the remaining 13 patients (group C) no suitable controls were available.

In a separate analysis (data not shown) patients and controls were matched using seven variables (age at the start of puberty, height SD score, and age at the start of GH treatment, GH dosage, sex, body mass index SD score at the start of GH treatment, and type of GH deficiency) where as much as possible variables were matched simultaneously. This strategy, however, led to different numbers of boys and girls in the two groups, because the best matching was found between different sexes in some cases.

We used as outcome parameters FH SD score, FH SD score-midparental height (MPH) SD score and FH SD score-height SD score at the start of puberty. In a multiple regression analysis of groups A and C these three outcome parameters were used as dependent variables. The age at the start of puberty minus the population mean for sex (3), height SD score at the start of puberty, GH dose and duration of GnRHa treatment were used as independent variables.

Results

Selected clinical data are shown in Table 1 [mean (SD)]. In groups A and C, the mean age at the start of GnRHa treatment was 12.8 (1.8) and 12.0 (1.9) yr, respectively, and the mean treatment period was 2.7 (range, 1.8–4.0) and 3.1 (range, 1.1–5.6) yr, respectively. The mean difference between the observed age at onset of puberty and the normative value was 1.2, 0.8, and 0.1 yr in groups A, B, and C, respectively.

In the analysis using seven matching variables we found comparable results for the outcome parameters, with a significant difference in FH SD score-MPH SD score between children treated with GH and GnRHa and their matched controls.

In the multiple regression analysis a significant negative correlation of height SD score at the start of puberty with the difference between FH SD score and height SD score at the start of puberty was observed ($P < 0.01$). No significant correlation was demonstrated for FH SD score or the difference between FH SD score and MPH SD score as dependent variables.

Discussion

We conclude that GHD patients who are at risk of not attaining their genetic growth potential by the relatively early onset of puberty can reach a FH close to their genetic target by the addition of GnRHa to GH substitution therapy. This effect was seen in both groups A and C. In contrast, continuing GH therapy alone, as in group B, leads to a FH of approximately 1 SD below target. The efficacy of the combination therapy is also shown by other relevant parameters such as the greater mean change in height SD score from the onset of puberty and, to a lesser extent, the change in height SD score since the onset of GH treatment. If the difference between FH SD score and MPH SD score is taken as the most

Abbreviations: FH, Final height; GHD, GH-deficient; GnRHa, GnRH agonist; MPH, midparental height.

TABLE 1. Summary of the clinical data [mean (SD)]

	Group A (n = 8)	Group B (n = 8)	Group C (n = 13)
Number (M/F)	5/3	5/3	0/13
Diagnosis			
Multiple/isolated GH deficiency	5/3	7/1	8/5
Idiopathic/organic GH deficiency	6/2	6/2	5/8
GH peak (mU/liter)	10.2 (5.4)	6.6 (6.0)	8.5 (4.8)
MPH SD score	−1.92 (0.81)	−0.89 (1.08)	−1.36 (1.22)
Age at start GH (yr)	8.9 (4.3)	6.8 (3.7)	9.0 (4.1)
H SD score start GH	−4.10 (1.43)	−3.78 (1.60)	−3.43 (1.97)
Age at start puberty (yr)	12.2 (2.2)	11.8 (1.3)	10.4 (2.4)
H SD score at start puberty	−3.02 (1.46)	−1.97 (1.19)	−2.68 (1.90)
GH dosage during puberty[a]	17.4 (2.8)	14.6 (4.9)	16.0 (3.8)
FH SD score	−1.75 (0.89)	−1.89 (1.16)	−1.34 (0.95)
FH SD score—MPH SD score	0.18 (0.86)[b]	−0.99 (1.25)	0.03 (1.19)
FH SD score—H SD score start puberty	1.27 (1.81)	0.08 (1.08)	1.34 (1.79)

[a] GH dosage: average in pubertal period (IU/m^2 · week, 1 mg = 3 IU).
[b] $P < 0.05$ compared with group B; in other variables, no significant differences between groups A and B.

reliable outcome parameter, the effect of GnRHa addition on FH can be estimated at 1 SD score (approximately 6–7 cm).

The literature on the final effect of the addition of GnRHa to GH in GHD children is limited. Adan *et al.* (4) reported that the combined treatment resulted in a normal adult height, albeit somewhat below target height. Hibi *et al.* (5) reported in 24 GHD children treated with GH and cyproterone acetate and/or medroxyprogesterone acetate for 4.4 yr that FH SD score was about 1 SD score higher than in a group children on GH alone. The FH SD score was −2.2 in boys and −1.9 in girls, somewhat lower than in the more recent studies. This may be due to less effective gonadal suppression by cyproterone acetate or medroxyprogesterone acetate (5).

In summary, despite the uncertainty about the representativeness of the patient sample studied by Mericq *et al.* (2), their data and those of other investigators discussed here, as well as our retrospective analysis, all point in one direction: adding GnRHa in early puberty to GHD patients who have been treated with GH, or in whom GH and GnRHa are started simultaneously, enables the patients to reach their genetic target, whereas FH of patients on GH alone is about 1 SD score below MPH SD score. This result is of similar size as the efficacy of GnRHa in idiopathic short stature (6).

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