Effect of Two-Year Growth Hormone (GH) Treatment in Children with Non-Endocrine Short Stature

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Abstract. Sixty-eight children with non-endocrine short stature (NESS) were treated with recombinant human growth hormone (GH) for two years. The patients consisted of 20 children with familial short stature (FSS; Group A), 17 children with small-for-date short stature (SFD; Group B), 5 children with combined FSS and SFD (Group A+B), and 26 children with idiopathic short stature (ISS; Group C). GH treatment significantly increased height velocity, height SD score (SDS), and height velocity SDS for chronological age (CA) in NESS. The mean height velocity was increased by GH treatment from 4.4cm/year to 7.1cm/year in the first year and 6.3cm/year in the second year, the mean height SDS from -3.07 SD to -2.63 SD in the first year and to -2.42 SD in the second year, and the mean height velocity SDS for CA from -1.66 SD to 1.62 SD in the first year and to 0.66 SD in the second year. Among the four groups, there was no significant difference in the effect of GH treatment judged by height velocity or height velocity SDS for CA. However, the treatment tended to be less effective in group A+B. There was no significant

Received: August 18, 1993

Accepted: October 12, 1993

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difference among the four groups in the increase in height SDS.

Seventeen children developed puberty during the two-year GH treatment: 7 in the first year and 10 in the second year. The mean height and age at the onset of puberty in 17 patients were 136.0 (± 9.7) cm and 12.23 (± 0.86) years in male, and 129.1 (± 5.5) cm and 11.3 (± 0.7) years in female patients, respectively. The height at the onset of puberty was shorter than that of normal children. Since it is known that children who develop puberty at short stature remain short, it is probable that the patients who developed puberty at short stature in this study will remain short as adults. The effect of treatment evaluated by the height SDS for BA was not improved. The effect of GH treatment in children with NESS should be carefully evaluated by conducting a long-term follow-up.

Key words: non-endocrine short stature, GH treatment, pubertal development

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Over the last several years, many investigators have reported that short-term GH treatment can at least increase the height velocity in short children with normal GH responses to provocative stimuli (1-15), whom we designated as non-endocrine short stature (NESS), although long-term treatment does not guarantee the attainment of full adult height, according to the multicenter study presented in San Francisco at the ESPE/LWPE joint meeting in 1993 (16). The final estimation of GH treatment should be judged by the final height attained. If there is an accurate method to predict final height, the estimation of GH treatment can be easily done. Several methods, such as Bayley-Pinneau (17), TW2 (18), and RWT (19) have been proposed for the final height prediction. However, these methods were made from the analysis of normal children and are not well applicable for short children. It is well known that the height at onset of puberty correlates well with the final height in normal children, GH-treated growth hormone deficiency, and untreated NESS (20-22). Therefore, we here report two-year GH treatment in children with NESS focusing on the height and age at onset of puberty.

Of particular concern in the GH treatment in children with normal GH secretion is the

possible adverse effect on glucose metabolism, since GH has a diabetogenic effect (23,24). Oral glucose tolerance tests (oGTT) are also analysed in this report.

Subjects and Methods

Patients

Of 78 children who entered this clinical trial, 68 completed two-year GH treatment. Ten children discontinued GH treatment, because of poor compliance in three cases, traffic accidents in two, removal to a remote locality or abroad in two, and bone fracture, lipoatrophy at injection sites, and myalgia in one case each.

All children were short (below -2 standard deviation {SD} of the mean height for age) and prepubertal before treatment. Before GH treatment, GH responses to two or more stimulation tests and spontaneous GH secretion during 3-hour nocturnal sleep were evaluated. They showed at least one normal GH response in stimulation tests: GH responses above 10ng/ml in the insulin test, arginine test, L-dopa test, or clonidine test, or above 15ng/ml in the glucagon-propranolol test. The 68 children who completed two-year treatment were classified into four groups: 20 children

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Table 1. Clinical Characteristics in Non-Endocrine Short Stature

	Male	Female	All
Case Number	48	20	68
Age (years)	8.75 $\pm$ 1.95	8.59 $\pm$ 1.94	8.75 $\pm$ 1.91
Bone Age (years)	6.70 $\pm$ 2.29	6.47 $\pm$ 2.26	7.24 $\pm$ 2.31
BA/CA Ratio (%)	75.6 $\pm$ 13.4	74.6 $\pm$ 13.5	77.9 $\pm$ 13.1
Height (cm)	111.7 $\pm$ 9.8	111.4 $\pm$ 10.1	111.5 $\pm$ 9.3
Height SDS (SD)	-3.06 $\pm$ 0.59	-3.02 $\pm$ 0.59	-3.05 $\pm$ 0.58
Height Age (years)	5.90 $\pm$ 1.62	5.82 $\pm$ 1.66	5.87 $\pm$ 1.53
Weight (kg)	19.2 $\pm$ 4.4	19.2 $\pm$ 4.6	19.2 $\pm$ 4.0
% Overweight (%)	-2.9 $\pm$ 8.4	-2.8 $\pm$ 8.0	-2.9 $\pm$ 9.6
Height Velocity (cm/yr)	4.4 $\pm$ 0.7	4.4 $\pm$ 0.8	4.4 $\pm$ 0.7
HV SDS for CA (SD)*	-1.73 $\pm$ 1.18	-1.52 $\pm$ 1.08	-1.67 $\pm$ 1.30

* Height velocity SD score for chronological age

with familial short stature (FSS, Group A), 17 children with small-for-date short stature (SFD, Group B), 5 children with combined familial and SFD (FSS+SFD, Group A+B), and 26 patients with idiopathic short stature (ISS, Group C). Familial short stature was diagnosed when the father was shorter than 157cm or the mother was shorter than 145cm, which was -2 SD for their generation, or when target height was below -1.5 SD, which is 162cm for boys and 150cm for girls. Target height was calculated by the method of Ogata *et al.* (25). SFD short stature was diagnosed when the birth weight was 1.5 SD below the mean.

Study protocol

Bone age was estimated by the TW2 method (20 bones) by one observer who was not otherwise involved in the study.

The onset of puberty was defined as the presence of a testicular volume of 4ml or more in boys and breast development Tanner stage

2 in girls. The age at onset of puberty was defined as the age at which these first pubertal signs were recorded in the case record forms.

All children received 0.5U/kg of hGH (Genotropin) subcutaneously 6-7 times a week. The 68 patients were followed prospectively for 2 years. Oral glucose tolerance test (oGTT) was performed before and every 6 months during GH treatment. Glucose tolerance was evaluated by the standardized scoring system for Japanese children (26). Immunoreactive insulin (IRI) was measured by RIA.

For statistical evaluation, Student's *t*-test, one-way analysis of variance (ANOVA) and Duncan's multi comparison were used. The results are presented as the mean $\pm$ SD.

Results

Table 1 shows the clinical characteristics and laboratory findings of 68 subjects. The mean height SD was approximately -3 SD.

Table 2. Clinical Characteristics in Four Groups of Non-endocrine Short Stature

	A FSS	B SFD	A+B FSS+SFD	C ISS	Significance ANOVA
Case Number	20	17	5	26	
Age (years)	9.28±2.18	7.86±1.92	8.07±2.05	9.06±1.62	**
Bone Age (years)	7.59±2.63	5.67±1.68	6.10±3.40	6.76±1.90	*
BA/CA Ratio (%)	79.7±12.4	74.3±9.8	72.0±24.5	73.9±13.5	NS
Height (cm)	114.6±11.1	106.9±9.1	107.6±8.9	113.3±8.3	**
Height SDS (SD)	-2.98±0.67	-3.19±0.64	-3.24±0.44	-3.01±0.52	NS
Height Age (years)	6.41±1.86	5.14±1.49	5.20±1.45	6.13±1.37	**
Weight (kg)	21.0±4.8	16.6±4.0	16.9±3.4	20.0±3.7	**
% Overweight (%)	0.1±7.6	-8.1±8.8	-7.1±10.0	-1.0±6.9	**
Height Velocity (cm/yr)	4.5±0.5	4.5±0.9	4.4±0.3	4.4±1.0	NS
HV SDS for CA (SD)*	-1.92±1.03	-1.79±1.42	-1.51±0.31	-1.58±1.25	NS
HV SDS for BA (SD)*	-1.98±1.23	-2.38±1.27	-2.69±1.35	-2.13±1.25	NS

* Height velocity SD score for chronological age

* Height velocity SD score for bone age

*p<0.05 **p<0.01 NS: not significant

Fig. 1a Change in height velocity before and during hGH treatment **Fig. 1c** Changes in height velocity SDS for CA before and during hGH treatment **Fig. 1b** Change in height SDS for CA before and during hGH treatment**Fig. 1** Changes in height velocity (a), height SDS for CA (b) and height velocity SDS for CA before and during hGH treatment.

The mean height velocity before treatment was 4.4cm and the mean target height SD score (SDS) was -0.96 SD. There was no significant difference between males and females in clinical characteristics and laboratory findings.

Table 2 shows the clinical characteristics of the four subgroups. Groups B and A+B were significantly younger and thinner than the other two groups. However, although there was no statistical difference in BA/CA ratio and height SDS among the four groups,

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Fig. 2 Change in height velocity before and during hGH treatment in four groups

Fig. 3 Height velocity in prepubertal and pubertal groups

Table 3. Bone age advancement

	1st year	2nd year	During 2 years
Prepuberty	1.52 ± 0.57 (39)	1.10 ± 0.42 (35)	2.57 ± 0.67 (42)
Puberty in the 2nd year	1.58 ± 0.83 (8)	1.13 ± 0.46 (6)	2.74 ± 0.94 (7)
Puberty in the 1st year	1.32 ± 0.70 (5)	1.50 ± 0.35 (4)	2.88 ± 0.91 (5)

Group A+B had the lowest values. Neither height velocity nor height velocity SDS for chronological age (CA) and for bone age (BA) was significantly different among the four groups.

As shown in Figure 1, GH treatment significantly increased height velocity, height SD score, and height velocity SDS for CA in NESS. The mean height velocity was increased by GH treatment from 4.4cm/year to 7.1cm/year in the first year and 6.3cm/year in the second year, the mean height SDS from -3.07 SD to -2.63 SD in the first year and to -2.42 SD in the second year, and the mean height velocity SDS for CA from -1.66 SD to 1.62 SD in the first year and to 0.66 SD in the second year. Among the four groups, there was no significant difference in the effect of GH treat-

ment judged by height velocity (Fig. 2) or height velocity SDS for CA. However, the treatment tended to be less effective in Group A+B. There was no significant difference among the four groups in the increase in height SD score.

Seventeen children developed puberty during the two-year GH treatment; 7 in the first year and 10 in the second year. When the patients were classified according to pubertal development, the pubertal children grew better than the prepubertal children, as shown in Figure 3.

Bone age advancement in Groups A, B, A+B and C during 2-year GH treatment was 2.54 ± 0.61 years, 2.65 ± 0.74 years, 1.20 ± 0.28 years, and 2.81 ± 0.78 years, respectively. Group A+B was significantly less advanced in

Fig. 4 Mean growth curve and height velocity in boys who developed puberty during first year (a) and second year (b). Shadow bar shows height velocity during puberty.

bone age, but only two patients were evaluated. Table 3 shows the bone age advancement among the groups divided by the timing of pubertal development. Bone age in children with pubertal development in the first year tended to advance faster in the second year of GH treatment, but the difference was not significant, due probably to the small number. Δ height age/ Δ bone age (Δ HA/ Δ BA) was 0.85 ± 0.54 at one-year and 1.10 ± 0.59 at two-year GH treatment. Mean height SDS for bone age before, at one-year and at two-year GH treatment was -0.93 ± 1.40 SD, -1.26 ± 1.26 SD and -1.32 ± 1.09 SD, respectively.

The mean height and age at the onset of puberty in 17 patients were $136.0 (\pm 9.7)$ cm and $12.23 (\pm 0.86)$ years in male, and $129.1 (\pm 5.5)$ cm and $11.3 (\pm 0.7)$ years in female patients, respectively. As shown in Figures 4 (a)(b) and 5 (a)(b), the mean height SD at

onset of puberty is still below -2 SD.

Figures 6 (a)(b) show the glucose and IRI pattern on oGTT before and during GH treatment. There was no significant difference in mean glucose pattern on oGTT before or during GH treatment. Two children showed a diabetic pattern on oGTT before GH treatment. However, the oGTT pattern in these children became a borderline pattern at 1 year and became a normal pattern in one and borderline in the other at two-year GH treatment. Although several children showed a borderline pattern, they did not remain at the same pattern during GH treatment and did not show an increased HbA1 level in any case. However, IRI increased significantly during GH treatment. There was a significant difference neither in the percentage of borderline patterns nor in the Σ IRI value among four groups before and during treatment. The

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Fig. 5 Mean growth curve and height velocity in girls who developed puberty during first year (a) and second year (b). Shadow bar shows height velocity during puberty.

Fig. 6 Blood glucose (a) and IRI (b) profiles (mean $\pm$ SEM) in oGTT before and during hGH treatment.

Σ IRI of oGTT increased during GH treatment and the Σ IRI of oGTT were significantly higher at the first year ($4270.1 \pm 2641.5 \mu\text{U/ml}$, $N=70$) and at the second year of GH treatment ($4192.3 \pm 2400.5 \mu\text{U/ml}$, $N=41$) than before treatment ($3426.9 \pm 1371.0 \mu\text{U/ml}$, $N=56$).

Discussion

Several variables such as height velocity, height velocity SDS for CA, height velocity SDS for BA and height SDS, are used for the evaluation of short-term GH treatment. Growth hormone treatment for two years in children with NESS significantly increased height velocity, height velocity SDS for CA and height velocity SDS for BA. Height SDS also improved. $\Delta\text{HA}/\Delta\text{BA}$ ratio is another variable to evaluate GH treatment. The $\Delta\text{HA}/\Delta\text{BA}$ ratio was below 1 in the first year and over 1 in the second year in this study. However, the relation between this ratio and the final outcome of GH treatment is unknown. The effectiveness of GH treatment judged by the increase in height velocity SDS for BA (more than 1.0 SD in the first year and more than 0 SD in the second year) was 94.2% in the first year and 66.7% in the second year.

The waning phenomenon, which is known to occur in GH treatment for GH deficiency, is also seen in the treatment of NESS, since the height velocity is lower in the second year than in the first year. Further, the effect on final height is still uncertain. The problem in evaluating the effect of GH treatment is that there is no established method to predict final height, which is the most important aim of GH treatment. Height SDS may be a factor predictive of final height by the projection method, which is widely used in Turner syndrome. The projected height method is useful in Turner syndrome because of the lack of spontaneous puberty in most patients with Turner syndrome. Since the patients with NESS develop puberty spontaneously, height SDS for BA may be a better predictor of final height. When the data were evaluated by the

height SDS for BA, the prognosis was not very promising. Although the height SDS for CA increases during GH treatment, the height SDS for BA decreases during two-year GH treatment.

For the final height prediction, height at onset of puberty was analysed, since height at onset of puberty has been reported to correlate well with the final height (20-22). Seventeen patients with NESS developed puberty during two-year GH treatment. The height at the onset of puberty is shorter than that of normal children. It is also known that the pubertal height gain (the increase in height from the onset of puberty till the final height) is shorter in children with late pubertal development than in those with early pubertal development (27). Therefore, it is suspected that once children develop puberty at short stature, the height deficit at the onset of puberty cannot be recovered during puberty. It is probable that the patients who developed puberty at short stature in this study will remain short as adults. The trial attempted to increase the pubertal height gain by increasing the GH dose during puberty: Stanhope *et al.* (28) report, however, that the prospective study did not show that increased GH doses at the onset of puberty made the final height taller; instead it induced a faster progression of puberty in GH deficiency.

There are at least two approaches to increasing the final height both in children with NESS by GH treatment and in children with GH deficiency. One is to increase the height at the onset of puberty to the same level as normal children. Early diagnosis is thus important to allow catch-up growth to optimal height before puberty. A high dose trial attempting to prevent the waning phenomenon is reported by Lesage *et al.* (29). They treated prepubertal short children with NESS using GH at a dose of 0.3U/kg/day , which is almost four times our usual dose, for two years and then stopped the treatment. During two-year high dose treatment, the patients gained 19cm in height on average and increased their height SDS for both CA and

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BA by 1.5 SD on average. The change in height SDS was minimal at one year after cessation of GH treatment and the patients developed puberty at near normal height. Although high dose GH treatment induced hyperinsulinemia, these metabolic changes were reversible.

The other approach is therapy combining GH and gonadotropin releasing-hormone (GnRH) analog in patients who have developed puberty while short in stature. Gonadal suppression treatment was reported (25,30) to be effective in GH deficiency in combination with GH. The gonadal suppression agents used in these reports were cyproterone acetate and medroxyprogesterone acetate. However, the effect of these agents on gonadotropins and sex steroids was insufficient and there were some side effects, such as adrenal suppression and obesity. Recently, several GnRH analogs have been used successfully to treat central precocious puberty without side effects. Although the effect of GnRH analog on the final height has not yet been confirmed in precocious puberty, the use of GnRH analog combined with GH treatment certainly appears to be appropriate.

It is reported that continuous GH infusions induce acute insulin resistance characterized by impaired suppression of hepatic glucose production and decreased insulin dependent glucose disposal (23,24). It is also known that acromegalic adults are frequently complicated with hyperinsulinemia and glucose intolerance, which is reversible after the successful treatment (31). Patients who showed a diabetic pattern or a borderline pattern on oGTT did not show an increased HbA_{1c} level. Two-year GH treatment did not impair glucose tolerance in NESS, although it increased insulin secretion. This result is in agreement with the study on GH-treated NESS (32) and GH-treated Turner syndrome (33).

In summary, two-year GH treatment in NESS was effective in increasing height velocity, height SDS for CA, height velocity SDS for CA and height velocity SDS for BA. There

was no difference in the effect of GH treatment evaluated in terms of the increase in height velocity SDS for CA among the four subgroups of NESS, although it tended to be less effective for FSS+SFD. However, evaluated in terms of the height SDS for BA, the effect was not improved. Therefore, the effect of GH treatment in children with NESS should be carefully evaluated by conducting a long-term follow-up, especially in children who develop puberty while still short in stature.

Acknowledgement

The authors are grateful to the Sumitomo Pharmaceutical Company Ltd. for providing Genotropin.

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