Effect of Growth Hormone on Total Cholesterol and Body Composition in Children with Non-Endocrine Short Stature, Partial Growth Hormone Deficiency and Growth Hormone Neurosecretory Dysfunction

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Abstract Total cholesterol (TC) level and percent ideal body mass index (%BMI) for age and height were measured in children with non-endocrine short stature (NESS)(n=11), partial growth hormone deficiency (PGHD)(n=4) and growth hormone neurosecretory dysfunction (GHND)(n=5) every 3 months for 2 years to evaluate the effect of growth hormone (GH) therapy. These measurements and annual growth rates were compared among three groups: group A (children who remained pre-pubertal during the study); group B (children who started puberty in the second year); group C (children who started puberty in the first year). There was no significant change in %BMI during the study period in the three groups and no significant correlation between %BMI and height velocity or height standard deviation (SD) before treatment or height gain after treatment. TC levels remained unchanged in groups A and B. However, there were significant decreases in group C after treatment. These results showed that the GH therapy in NESS, PGHD and GHND children had no effect on cholesterol metabolism or body composition, and that the children's nutritional status did not affect their natural growth.

Key words: short stature, growth hormone, body mass index, total cholesterol

Introduction

GH has a potent effect on carbohydrate, lipid, and protein metabolism. Children with GH deficiency have an increased fat mass, which is reduced by GH treatment (1). In adults, GH deficiency is also associated with an

increase in fat and a decrease in muscle mass (2), and they are at increased risk for developing cardiovascular disorders. This may be because GH has a role in the control of lipoprotein metabolism (3). GH treatment increases lean body mass and decreases fat mass (4). These results lend support to the necessity of life-long use of GH therapy in patients with complete growth hormone deficiency. However, most children who are treated with GH because of short stature in Japan do not have

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complete GH deficiency, but they are patients with NESS, PGHD and GHND.

Children with NESS are leaner than the normal population (5). It is known that obese children have reduced spontaneous GH secretion (6), but even within the normal range, body mass index is inversely related to GH secretion in normal and short stature children (7).

The present study was undertaken to attempt to evaluate the effect of GH therapy on body composition and serum cholesterol in children with NESS, PGHD and GHND. The role of body mass and the effect of age on the response to growth hormone therapy were also studied.

Subjects and Methods

Patients

Twenty children with short stature who were below -2 SD from the mean height for age (15 males and 5 females) were enrolled in the study. They were classified into three categories (NESS 11, M/F=8/3, 10.0 ± 2.4 year. PGHD 4, M/F=4/0, 12.9 ± 1.7 year. GHNSD 5, M/F=3/2, 11.0 ± 0.8 year.) based on the results of provocation tests of growth hormone secretion and the excretion of urinary growth hormone (8). Recombinant human growth hormone (hGH) was administered subcutaneously at a dose of 0.5 U/kg, divided into 4 to 6 doses per week. They were followed-up every 3 months for two years and divided into three groups in regard to their pubertal status during the study. The onset of puberty was defined as a testicular volume of 4 mL or more in boys and breast development to Tanner stage 2 in girls.

Group A: children who remained prepubertal during the study. (n=7, mean age 9.5 ± 2.2 year, M:F=6:1, NESS 5, PGHD 1, GHNSD 1)

Group B: children who entered puberty in the second year (n=6, mean age 10.4 ± 1.7 year, M:F=5:1, NESS 4, PGHD 1, GHNSD 1).

Group C: children who entered puberty in the first year (n=7, mean age 12.6 ± 1.4 year, M:F 4:3, NESS 2, PGHD 2, GHNSD3)(Table 1).

Methods

Auxological measurements and serum total cholesterol levels were recorded at every visit. Body mass index (BMI), the ratio of weight (kg) and height² (m²), and %BMI (BMI expressed as a percentage of the BMI of a child of the same age whose weight and height were on the 50 th centiles, and of the same height whose weight was on the 50 th centiles) were determined for each child. They were expressed as %BMI for age and %BMI for height, respectively. Changes of the above measurements were compared and the relationship between %BMI and height SD, growth velocity, Δ height SDS, and serum total cholesterol levels were analyzed. The net height gain was compared in group A between the children who started GH treatment under 10 years of age and above 10 years of age.

Statistics

Results were expressed as the mean $\pm$ SD. The unpaired student t test was used for the difference of net height gain in group A. The relationships between %BMI and height SD, growth velocity, Δ height SDS, and serum total cholesterol level were analyzed by linear regression. Comparisons of group mean para-

GH Effect on TC and BMI in NESS, PGHD and GHND

meters and tests for significant differences among the means of total cholesterol, %BMI for age and height were made at every attendance using analysis of variance and Bonferroni adjustment to the p values. The level of statistical significance was taken as $p < 0.05$.

Results

Subjects characteristics (Table 1)

Table 1 shows the characteristics of each group. The chronological age of group C was significantly older than group A. %BMI for age was under 100% in all groups, but %BMI for height varied among three groups. %BMI for age in group C was smaller than in the other groups and %BMI for height and obesity index was also significantly smaller in group C than group B. There were no significant differences in height SD, serum total cholesterol levels or growth rates before GH therapy among three groups.

There was no correlation between %BMI for age or height and height SD, growth rate, Δ height SDS and total cholesterol level in all groups.

Changes of serum total cholesterol levels (Fig. 1)

There was no significant change in total cholesterol level during the study in groups A or B. In group C, serum total cholesterol decreased significantly after GH therapy. %BMI for age and height remained unchanged throughout the study in all groups. Changes of %BMI varied in each individual. When expressed as %BMI for age, 3 out of 20 children were above 100% and as %BMI for height, 9 out of 20 were above 100%.

Height gain after GH treatment (Table 2, Fig. 2)

In group A, the growth rate of children under 10 years of age decreased in the second year, and net height gain(height velocity after GH treatment minus height velocity before therapy; cm/year) when compared with the children who started GH therapy above or under 10 years, did not change in the first year (3.0 ± 1.8 vs. 2.3 ± 0.3 , not significant (NS)), but there was much difference in the second year (2.7 ± 1.2 vs. 0.2 ± 1.3 , $p < 0.05$). There was no significant difference between the two groups in terms of total cholesterol and %BMI for age and height.

Table 1 Subjects Characteristics.

Group (n)	M/F	CA (SD)	Height SD (SD)	%BMI for age (SD)	%BMI for height (SD)	Obesity Index (SD)	TC (mg/dl) (SD)	Growth rate (cm/yr) (SD)
A (7)	6/1	9.5 (2.2)	-3.20 (1.08)	92.20 (12.21)	98.49 (9.76)	-1.60 (9.89)	170.0 (24.9)	4.1(0.9)
B (6)	5/1	10.4 (1.7)	-2.93 (0.5)	94.96 (4.72)	105.31 (6.75)	4.20 (5.94)	175.7 (15.9)	4.3(0.6)
C (7)	4/3	12.6 (1.4)	-2.57 (0.68)	82.50 (6.03)	90.75 (5.68)	-9.09 (5.69)	185.5 (20.3)	4.1(1.2)

∴: $P < 0.05$. CA: Chronological Age(yrs), TC: Total cholesterol(mg/dl)

Fig. 1 Changes in serum total cholesterol level in each group after growth hormone therapy.

Table 2 Net height gain after GH therapy compared with pretreatment growth rates.

Year of Therapy	Net Height Gain(cm/yr)		P
	≥10 yr (n=3)	<10 yr (n=4)	
First	2.3 ± 1.8	2.3 ± 0.3	NS
Second	2.7 ± 1.2	0.2 ± 1.3	<0.05

Fig. 2 Growth rate before and after GH therapy. (○; ≥10 year, ◆; <10 year)

Discussion

Our study showed that children with NESS and PGHD were leaner than normal and that their age was important in regard to the response of GH therapy. There was no correlation between %BMI and height SD, growth velocity, total cholesterol level, delta height

SDS and %BMI for age. The height and total cholesterol levels did not change after GH treatment in our study.

Other investigators have reported that children with idiopathic short stature are leaner than normal and have showed that BMI is positively correlated with height, height velocity and plasma insulin-like growth factor I (IGF-I)(9). Adequate nutrition is considered to be necessary for the action of GH on plasma IGF-I and the growth-promoting action of IGF-I. This may influence the basal situation and the response to hGH therapy. Variations in the growth response of the hGH-treated idiopathic short stature children may partly be explained by variations in their nutritional intake. Martha (10) reported that pretreatment BMI-SDS (expressed as standard deviation score for age) did not correlate with either growth velocity or serum IGF-I, but after 12 months of GH therapy, BMI-SDS correlated positively with changes in plasma IGF-I and growth velocity; BMI-SDS did not change during treatment. It is thought that the association with increased growth hormone binding protein, a higher absolute GH dose, and a high GH dose relative to endogenous production contributed to the correlation between BMI and growth response. Since BMI does not reflect body fat mass, a bio-electrical impedance method and magnetic resonance imaging were used to evaluate the effect of GH on the change in adiposity in the children with growth hormone deficiency (11, 12)

There was no correlation between %BMI for age and height and height SD, growth velocity, total cholesterol level, and delta height SDS after GH in this study. When expressed as %BMI for age, 3 out of 20 children were above

100% and as %BMI for height, 9 out of 20 were above 100%. There was heterogeneity in our study for age, gender, and body composition of the patients. A longer study would be needed to elucidate the mechanism of the variations in growth response to GH.

Hypercholesterolemia in children with constitutional growth delay has been reported and there is a negative correlation between the serum total cholesterol and annual height gain (13). In adult GH deficient patients, there is a significant decrease in plasma cholesterol after 6 months of GH therapy (14) but Whitehead *et al.* found no change (15). Edén reported increased high density lipoprotein (HDL)-cholesterol and decreased low density lipoprotein (LDL)-cholesterol levels after GH therapy in adults with GH deficiency (16). There was no change in total cholesterol during the study in groups A and B. GH treatment had no apparent effect on increase in lipolysis sufficient to reduce the total cholesterol to that of children with NESS and PGHD. It is considered that these children with NESS, PGHD and GHND may have sufficient GH secretion to regulate cholesterol metabolism. In group C, The total cholesterol levels decreased after GH therapy, and since they entered puberty during the first year, this phenomenon was probably an effect of sex steroids.

The response to GH therapy in the children who started the GH before 10 years of age was lower than in children above 10 years of age in group A. This difference seemed to be due to differences in the basal level of sex steroids before the onset of puberty. Since it is known that the response of GH treatment lessens each year (17), it is suggested that the dose of hGH should be increased every year in

younger children until pubertal development starts.

To achieve the optimal response to GH therapy, it is important to consider the relationships between age, body mass and nutritional state in children with NESS and PGHD.

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