Growth Response to Growth Hormone Therapy in Patients with Different Degrees of Growth Hormone Deficiency

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The Executive Scientific Committee of the International Cooperative Growth Study (ICGS) Japan

Abstract. Growth response to GH therapy in prepubertal patients with idiopathic GH deficiency (GHD) was analyzed in terms of the chronological age at the start of GH treatment and the GH secretory capacity, by using the large database provided by the International Cooperative Growth Study (ICGS) Japan. 1192 patients, aged from 3 to 10 years were divided into three groups with the following maximum GH values in GH stimulation tests: Group A: both ≤ 5 ng/ml, group B: both 5–10 ng/ml, group C: one > 10 ng/ml. Analysis of age-related growth response using with delta height SDS (Δ height SDS) as a response variable revealed that the group A patients responded better to GH, while there was no differences between the other groups. Simple and multiple regression analysis showed that IGF-I and chronological age (CA) negatively correlated with growth response, and target height SDS — height SDS positively correlated. These three most important predictors accounted for 49% of the variation in the growth response in group A, whereas six variables such as CA, frequency of GH injection, % overweight, GH dose, target height — height SDS, and pretreatment height velocity SDS accounted for only 28% of those in groups of B and C. These results lead us to conclude that growth response to GH is related to the degree of GH impairment with its cut-off level of 5 ng/ml. From these findings it might be suggested that treatment regimen should be tailored to individual requirements according to the degree of GHD.

Key words: GH deficiency (GHD), Non-GHD, GH, Growth response, High-dose GH therapy

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IMPAIRED GH secretion leads to slow growth in childhood and permanent short stature in adult life. Historically, impaired GH secretion has been defined as the inability of GH concentrations to exceed certain levels during GH stimulation tests [1]. The criteria for initiation of GH treatment in children have been discussed during three decades of experience with GH therapy in Japan [2–4]. The level of such a cut-off is set currently at 10 ng/ml for the maximum GH level during a standard provocation test. Nevertheless, it has not yet been determined whether children with different extents of GH deficiency (GHD), from classic GHD to those who have insufficient GH, could achieve similar growth response to GH, but this issue has never been extensively studied in a larger group of patients. Furthermore, one might argue that the current method of treatment is not sufficient to enhance growth and achieve a better final height [5, 6].

We will herein therefore review the current knowledge about GH therapy in the patients with different extents of GHD analyzed on the basis of the data, in the large database provided by the International Cooperative Growth Study (ICGS) Japan. Furthermore, in order to clarify the factors influencing the response to GH, a multiple regression approach was used to determine which factors best predicted the first year growth response in this cohort of children.

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On the basis of an analysis of the current GH therapy situation, the use of higher doses of GH as a method of treatment will be discussed for reference in future GH therapy.

Subjects

From the total ICGS database on 5473 patients with idiopathic GHD, 1192 newly treated patients were selected according to the following inclusion criteria: 1) documented prepubertal idiopathic GHD met the criteria of the Foundation for Growth Science for GH treatment; 2) completed at least one year’s treatment; 3) chronological age (CA) age ≥ 3 yrs, < 11 yrs for boys and girls. For further analysis these patients were divided into three groups according to maximum peak GH values after pharmacological stimulation tests; group A: = 5 ng/ml (n=139), group B: < 5 to = 10 ng/ml (n=494), group C: > 10 ng/ml (n=559).

Methods

Response variable and parameters from auxological data, GH secretory capacity, method of treatment and growth response

14 various parameters from the auxological data, GH secretory capacity, treatment method and growth response were selected and delta height (ΔHT) SDS was chosen as a response variable. These 14 parameters were sex, birth length SDS, birth weight SDS, CA at the start of GH, % overweight, height SDS, height velocity (HV) SDS, target height (tHT) SDS, target height (tHT) SDS — height (HT) SDS, IGF-I, GH max, mean sleep GH, GH dose (IU/kg/wk), frequency of GH injection.

Growth parameters, such as HT SDS, HV and HV SDS were calculated. For these calculations of SDS, the Japanese standard for height and height velocity by Suwa et al. [7, 8] was used. tHT SDS and tHTSDS — HT SDS were calculated by the method according to Ogata et al. [9]. The % overweight at the start of GH treatment was calculated from the patient’s weight expressed as a percentage of the median weight of individuals with the same height as the patient in a normal population using the method of Murata et al. [10]. Data were presented as the median and the 10th and 90th percentiles or the mean ± SD.

Statistical analysis

The analysis of the growth response to GH treatment during the first year is based on a regression analysis between a response variable of ΔHT SDS and 14 other parameters. Statistical significance was determined by Student’s t-test and one-way analysis of variance (ANOVA) with Duncan’s multiple comparison method and Pearson’s correlation coefficients.

Multiple regression analysis was performed by the stepwise method which was an ‘all possible approach’ using Mallows C(p) as the criterion for choosing predictors as described by Weisberg [11]. This was analyzed with data from the patients having all eight potential predictors such as CA, % overweight, HT SDS, tHT SDS — HT SDS, GH max, IGF-I, GH dose and frequency of GH injection.

Results

Patients’ characteristics at birth and at the start of GH treatment

Some auxological characteristics at birth and at the start of GH treatment of three groups of patients investigated are given in Table 1. Median birth length SDS, birth weight SDS, HT SDS and tHT SDS were below normal for all the patients, irrespective of hormonal deficiencies. HT SDS value in group A were significantly smaller than those in group B and group C, whereas birth length SDS and tHT SDS were significantly greater. There were no significant differences among three groups with respect to chronological age and birth weight SDS. Also there were no differences between group B and group C in these indices. These results indicate that those in group A are much more severely growth retarded, but groups of B and C have some characteristics of retarded fetal growth and short parents.
Age-related growth response in the patients with different degrees of GHD

Age-related growth response to treatment with GH during the first year, expressed in terms of ΔHT SDS, is given in Fig. 1. The results show that the patients with most severe GHD (group A) responded better to GH, while there was no difference between other groups. The response to GH was related to the degree of GH impairment, and the level of cut-off is defined as 5 ng/ml in the stimulation tests. These results indicate that severe GHD defined by stimulation test is clearly distinguished from other types of GHD in terms of growth response. Group B and group C are indistinguishable, but age-related growth response in each group was not clear from this analysis.

Correlation between ΔHT SDS and 14 parameters from growth, GH secretory capacity and method of treatment

The results of the simple regression analysis are given in qualitative terms in Table 2. It can be seen that chronological age, HT SDS at the start of treatment, mid-parental height SDS (i.e. tHT SDS), and birth length SDS from auxological parameters and GH max, sleep GH, and IGF-I(log) from GH secretory capacity were recognized as important variables in group A. Chronological age, HT SDS, and indices of GH secretory capacity were negatively correlated with the growth response, and the tHT SDS and tHT SDS — HT SDS were positively correlated. This implies that the younger the patients, the taller the patient’s parents, and the more severely impaired the GH secretory capacity, the better was the therapeutic effect achieved. In groups B and C only chronological

Table 1. Auxological characteristics at birth and at the start of GH treatment in prepubertal children with idiopathic GHD

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW SDS</td>
<td>-0.28 134</td>
<td>-0.41 483</td>
<td>-0.40 545</td>
</tr>
<tr>
<td></td>
<td>(-1.55 ~ 0.91)</td>
<td>(-1.74 ~ 0.85)</td>
<td>(-1.82 ~ 0.73)</td>
</tr>
<tr>
<td>BL SDS</td>
<td>-0.26 87</td>
<td>-0.59 308</td>
<td>-0.79 354</td>
</tr>
<tr>
<td></td>
<td>(-1.47 ~ 0.59)</td>
<td>(-2.35 ~ 0.59)</td>
<td>(-2.37 ~ 0.42)</td>
</tr>
<tr>
<td>Start of GH treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>7.17 139</td>
<td>7.08 494</td>
<td>7.00 559</td>
</tr>
<tr>
<td></td>
<td>(3.83 ~ 10.33)</td>
<td>(4.42 ~ 10.42)</td>
<td>(4.75 ~ 10.17)</td>
</tr>
<tr>
<td>HT SDS</td>
<td>-2.97 131</td>
<td>-2.69 489</td>
<td>-2.79 559</td>
</tr>
<tr>
<td></td>
<td>(-4.43 ~ 2.07)</td>
<td>(-3.75 ~ 2.03)</td>
<td>(-3.85 ~ 2.07)</td>
</tr>
<tr>
<td>%Overweight</td>
<td>0.30 133</td>
<td>-2.60 485</td>
<td>0.30 133</td>
</tr>
<tr>
<td></td>
<td>(-12.50 ~ 13.70)</td>
<td>(-12.20 ~ 9.90)</td>
<td>(-12.50 ~ 13.70)</td>
</tr>
<tr>
<td>tHT SDS</td>
<td>-0.23 131</td>
<td>-0.66 486</td>
<td>-0.77 546</td>
</tr>
<tr>
<td></td>
<td>(-1.48 ~ 0.75)</td>
<td>(-1.58 ~ 0.21)</td>
<td>(-1.48 ~ 0.21)</td>
</tr>
</tbody>
</table>

Data are shown as median and 10th and 90th percentiles.

Fig. 1. ΔHT SDS observed after 1 year of GH treatment, according to CA at the start of GH. ΔHT SDS represented as median (—), interquartile (box plot) and 10th and 90 th percentiles.
age was recognized as a significant variable.

**Multiple regression analysis**

In order to define the important predictor for the growth response, multiple regression analysis was performed. In a multiple stepwise regression analysis, IGF-I(log), chronological age and tHT SDS-HT SDS were the most important variables in the prediction of individual growth response to GH treatment. With these three measures, 49% of the growth response during the first year of treatment could be predicted in severe GHD, as shown in Table 3, whereas six variables such as chronological age, frequency of GH injections, % overweight, GH dose, tHT SDS—HT SDS and pre-treatment HV SDS accounted for only 28% of those in groups of B and C (Table 4).

**Discussion**

Growth response to GH in the patients with different degrees of impaired GH secretion was investigated by using the large database from ICGS Japan. Analysis of age-related growth response to
GH revealed that the response to GH is related to the degree of GH impairment—as defined by pharmacological stimulation test results with a cut-off level of GH max at 5 ng/ml. Previous analysis with similar ICGS database also suggested that therapeutic effect judged by the change in height velocity SDS was higher in the group with mean peak GH less than 5 ng/ml than in the other groups [3, 4]. Grouping children into those with “classic” GHD, those who have insufficient GH, and those who are healthy but of short stature is artificial. These studies agree, however, that severe GHD with a GH max less than 5 ng/ml could be clearly distinguished from other groups of GHD in terms of auxological characteristics and first-year growth response. Furthermore, it is noteworthy that insufficient GHD with a GH max less than 10 ng/ml could be clearly distinguished from other groups of GHD in terms of auxological characteristics and first-year growth response. In order that children with GHD reach the goal of normal adult stature, methods of treatment need to be improved. Simple and multiple regression analysis was performed in both groups of severe GHD and other GHD to determine both auxological factors characterizing the patients and the factors related to the chosen methods of treatment which are of significance for the observed magnitude of the growth response. It has been observed that the magnitude of the growth response in severe GHD positively correlated with target height SDS and target height SDS — height SDS, and negatively correlated with age and GH secretory capacity. This implies that the younger the patients, the taller the patient’s parents, and the more severely impaired the GH secretory capacity, the better is the therapeutic effect achieved. It is, however, a little surprising to find that the frequency of GH injections during the week and the total GH dose were not significantly correlated. This is in contrast with other analyses already reported [12, 13]. This may be due to the narrow range of frequency of injections and doses of GH administered to this cohort of patients. In the patients with severe GHD, three predictors such as IGF-I, chronological age and target height accounted for 49% of the variability of the response in terms of ΔHT SDS. At present, this analysis of data suggests that, during the first year of treatment, response to GH is influenced by the magnitude of GH secretion, in accordance with the published reports [13, 14].

The observation that chronological age at the start of GH therapy is an important determinant

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>P</th>
<th>Explained variability</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA at start of GH</td>
<td>-0.065</td>
<td>0.004</td>
<td>0.0001</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>GH inj./w</td>
<td>0.027</td>
<td>0.007</td>
<td>0.0001</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>%Overweight at start of GH</td>
<td>0.004</td>
<td>0.001</td>
<td>0.0001</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>GH dose</td>
<td>0.536</td>
<td>0.149</td>
<td>0.0003</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>tHT SDS — HTSDS at start of GH</td>
<td>0.027</td>
<td>0.010</td>
<td>0.0089</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>Pretreatment HV SDS</td>
<td>-0.018</td>
<td>0.006</td>
<td>0.0014</td>
<td>&lt;1</td>
<td>6</td>
</tr>
</tbody>
</table>

Total variability (R²) (n=870) 28%
of the first year response is in line with the findings of other investigators [12, 13].

It is noteworthy that the relative gain in height at the end of the first year on GH was greater in young (=shorter) children. This means that, indeed, the process of catch-up in height induced by GH is more pronounced in younger children, strongly supporting the frequency advocated importance of an early diagnosis and treatment of GHD.

In contrast, in mild and non-GHD, six predictors such as chronological age, frequency of GH injections, % overweight, GH dose, tHT SDS−HT SDS and pretreatment HV SDS accounted for only 28% of the variability. This suggests the need to improve the methods of treatment for this groups of children. It needs to be emphasized, however, that the present observations cannot be generalized on beyond the first year, since during the first year of GH treatment the process of growth is probably governed by an increased responsiveness to GH. Nevertheless, the extension of this analytical approach indicates that in the future GH treatment of patients with different degrees of GHD should be tailored to individual requirements.

There is now sufficient evidence that GH given in doses somewhat higher than given to GH deficient children not only increases height temporarily, but also leads to a substantial increase in expected adult height [15–20]. The use of higher dose of GH may therefore be advocated to improve better final height. In line with this notion, clinical trials for GH treatment with the higher doses of GH featuring either a high dose from the onset or a step-wise increase in the dose during the first three years are currently being conducted in Japan. In clinical trial with GH dose of 1 IU/kg/w and 1.5 IU/kg/w, patients treated with higher doses of GH attained a greater growth rate SDS than that patients with a conventional GH dose of 0.5 IU/kg/w. It was observed that the period for gaining 1 SD in height in the high-dose group is much shorter than in the conventional control group.

In a catch-up growth study in which the GH dose was increased 0.25 IU/kg/w annually from 0.5 IU/kg/w during the three year study period, the annually increased dosage group also showed significantly higher growth rate and its SDS in the second and third years. More advantageous in this group was the annual gain in height SDS. The mean height SD scores achieved after 36 months of treatment were −1.40 SD in the increased dosage group, but −2.02 SD in the control group. The period required to gain 1 SD in height in the annually increased dosage group was much shorter than in the historical control group. In both treatment regimens, there was no significant difference between the two groups in the acceleration of bone maturation. With higher doses of GH, there is legitimate concern about untoward effects on endocrine function, and particularly about the development of insulin resistance and carbohydrate intolerance. Nevertheless, glucose intolerance was not observed in repeated oGTTs, while IRI increased in parallel with the increase in the GH dosage. Physical and other laboratory examinations gave no abnormal results during the study period, so that GH therapy featuring either the high dose or step-wise increase of dosage during the first three years gives us promising results which indicate how to promote the better height gain than with the conventional GH therapy by minimizing the waining phenomenon. Further study is required to substantiate our preliminary data and enables us to form definite conclusions, not only regarding better final height, but also regarding effects on GH-related parameters such as IGF-I, lipid and carbohydrate metabolism.

Nevertheless, if the results of large clinical trials are positive, it remains entirely possible that treatment strategies will be progressively modified.

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References
