Effect of growth hormone therapy on Taiwanese children with growth hormone deficiency

Ying-Hua Huang a,c, Yau-Yau Wai b, Yang-Hau Van a, Fu-Sung Lo a,*

a Department of Pediatrics, Chang Gung Memorial Hospital, Chung Gung University College of Medicine, Taoyuan, Taiwan
b Department of Radiology, Chang Gung Memorial Hospital, Chung Gung University College of Medicine, Taoyuan, Taiwan
c Department of Pediatrics, Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Received 26 February 2011; received in revised form 9 June 2011; accepted 9 June 2011

KEYWORDS
growth hormone deficiency; growth hormone therapy; isolated growth hormone deficiency; multiple pituitary hormone deficiency; transient growth hormone deficiency

Background/Purpose: Human growth hormone (GH) has been successfully used in children with GH deficiency (GHD). However, there are few published data on the effect of GH in Taiwanese children with GHD.

Methods: We performed a retrospective cohort study to identify factors influencing the effect of GH therapy on ethnic Chinese children with GHD in Taiwan. Idiopathic GHD can be classified into isolated GHD (IGHD) and multiple pituitary hormone deficiency (MPHD). The study looked at the effect of GH on the auxological, biochemical, and imaging parameters of 51 patients (13 girls and 38 boys) in three different diagnostic groups: MPHD (n = 12), IGHD (n = 8), and transient GHD (TGHD; n = 31). TGHD is defined as a GH peak >10 μg/L in re-evaluation by two GH stimulation tests approximately 6 months after discontinuation of GH therapy.

Results: The height velocity for first-year GH therapy was 7.61 ± 1.46, 8.14 ± 1.92, and 9.99 ± 2.75 cm/y in the TGHD, IGHD, and MPHD groups, respectively. After post hoc comparison, the MPHD group had a significantly accelerated height velocity in the first year compared to the TGHD group. Correlation analysis showed that a change in height standard deviation score (SDS) in the first year had a significant negative correlation with the following variables: peak GH (r = −0.52, p < 0.001), pretreatment height SDS (r = −0.49, p < 0.001), and height-target height (HT-TH) SDS (r = −0.49, p < 0.001). Change in height SDS in the first 2 years had a significantly negative correlation with peak GH (r = −0.51, p < 0.001), insulin-like growth factor-1 SDS (r = −0.35, p = 0.022), height SDS (r = −0.60, p < 0.001), difference between bone age and chronological age (r = −0.46, p = 0.001), and HT-TH SDS (r = −0.50, p = 0.001). After using multiple linear regression, the pretreatment GH peak value was found to be significantly associated with height increments after 1 year of GH treatment (B = −0.07, p = 0.014).
Introduction

For more than 50 years, human growth hormone (GH) has been used in GH deficiency (GHD). There are few published data reporting factors predicting the effect of GH on Taiwanese children with GHD. The conventional study of GH secretion, diagnosis, and treatment of GHD during childhood and adolescence is still controversial. The diagnosis of GHD is a multifaceted process requiring comprehensive clinical and auxological assessment, combined with the biochemical testing of the GH—insulin-like growth factor (IGF) axis and evaluation with brain magnetic resonance imaging assessment. We also suggest that patients with GHD, specifically IGHD, must undergo a re-evaluation of GH secretion after completion of GH therapy.

The etiology of GHD may be idiopathic or associated with organic causes, such as tumor, surgery, or irradiation of the sellar area. Idiopathic GHD may be classified into isolated GHD (IGHD) and multiple pituitary hormone deficiency (MPHD) by its association with a deficiency of one or more anterior pituitary hormones during provocation tests. Morphological alterations on brain MRI in patients with GHD include pituitary hypoplasia, absence or interruption of the pituitary stalk, and an absent or ectopic posterior lobe.

Most subjects previously labeled as having IGHD with a normal pituitary MRI or an isolated small pituitary gland have been reported to show a normalization of GH secretion after completion of GH therapy. Most patients with MPHD have a low height, peak GH level, and IGF-1 standard deviation score (SDS) and greater bone age (BA) delay than partial those with IGHD or severe IGHD before GH therapy. In this investigation, we performed a retrospective cohort study of the effect of GH on the auxological, biochemical, and imaging parameters of 51 ethnic Chinese children in three different diagnostic groups of GHD (TGHD, IGHD, and MPHD) and analyzed the variables predicting the response to GH treatment.

Patients and methods

Patients

The retrospective cohort study comprised 51 patients (13 females and 38 males) with GHD who were receiving GH treatment and were followed up in the Division of Pediatric Endocrinology and Genetics at Linkou Chang-Gung Memorial Hospital from Aug 1996 to July 2010. Patients presenting the following criteria were diagnosed as having GHD: (1) peak GH response less than 10 μg/L after two GH provocation tests (insulin and clonidine stimulation test); (2) severe short stature (height < 3rd centile) or low height velocity < 4 cm/year; and (3) BA retarded by at least 2 SDS from the chronological age (CA). The height of the patient is expressed as an SDS (see the supplementary methods), and the report of the Department of Physical Education and Sports of the Ministry of Education in Taiwan was used as to define the standards.

Anterior pituitary function was evaluated by combined pituitary function testing: insulin tolerance test for GH and cortisol secretion; thyrotropin-releasing hormone test for thyroid-stimulating hormone (TSH) and prolactin secretion; and gonadotropin-releasing hormone test for follicle-stimulating hormone and luteinizing hormone secretion (see the supplementary methods). None of the patients received sex steroid priming before the GH stimulation tests.

Methods

Based on the results of endocrinological evaluation, patients were divided into three groups: (1) patients with MPHD (n = 12), defined as GH peak concentration < 10 μg/L accompanied by a deficit of one or more anterior pituitary hormones; (2) patients with IGHD (n = 8), defined as a GH peak < 10 μg/L; and (3) patients with TGHD (n = 31), defined as a GH peak >10 μg/L on re-evaluating GH status by pharmacological stimulation (insulin stimulation test or clonidine test) approximately 6 months after discontinuation of GH therapy considering the initial diagnosis as MPHD (n = 2) or IGHD (n = 29) (Fig. 1).

MRI was performed after diagnosis of GHD for 50 patients (see the supplementary methods). The one remaining patient underwent a brain computed tomography study. All images were evaluated by one radiologist. The height of the pituitary gland was measured on the midline sagittal plane perpendicular to the floor of the sella turcica to the highest point of the surface of the superior gland, located at the point of insertion on the pituitary stalk. The presence of the stalk was determined, and its width was evaluated on both the coronal and sagittal images. The stalk was classified as normal or as showing dysgenesis [including being thin (<2.13 mm), interrupted, or absent]. The bright spot of the posterior pituitary was evaluated in both the coronal and sagittal images. It was considered to be ectopic if located outside the sella turcica. The age of the 50 patients at the time of MRI ranged from 3.21 to 19.12 years (10.69 ± 3.24 years).

In the MPHD group, two patients had GHD accompanied by TSH, adrenocorticotropic hormone, and gonadotropin deficiency, two had GHD with TSH and gonadotropin deficiency, three with TSH deficiency alone, two with
antidiuretic hormone deficiency, two with gonadotropin
deficiency, and one with adrenocorticotropic hormone
deficiency. These patients were treated with appropriate
hormone replacement. Sex steroid replacement therapy
was considered in patients with gonadotropic hormone
deficiency and poor secondary sexual development despite
an appropriate BA having been achieved (13 years in boys
and 12 years in girls).14

In this study, the expense of the GH therapy used for all
the patients with GHD was qualified and paid by Bureau of
National Health Insurance, Department of Health, Execu-
tive Yuan, Taiwan. All the patients received the fixed dose
0.48 IU/kg/wk (0.16 mg/kg/wk) of recombinant GH, from
either Saizen (Merck Serono, Modugno, Italy), Norditropin
(Novo Nordisk A/S, Bagsvaerd, Denmark), or Genotropin
(Pfizer Inc., Puurs, Belgium). GH was divided equally into
daily doses and administered subcutaneously before sleep.
All the patients received GH therapy for at least 1 year. The
continuous application of GH replacement therapy was
qualified by the Bureau of National Health Insurance
annually, and the criteria were such that the minimum
height velocity after GH therapy was to be $>2$ cm/y
measured before initiating GH therapy and skeletal
age $<16$ years in boys and $<14$ years in girls.14

A total of 48 patients underwent a re-evaluation of GH
status using one or two pharmacological stimuli (insulin
stimulation or clonidine test) at least 6 months after
discontinuation of GH treatment. If the GH peak level in
any one GH re-evaluation was observed to be more than
10 $\mu$g/L, the patient was reallocated to the TGDH group
from his or her initial diagnostic group (IGHD or MPHD).

Statistical analysis

Continuous data were presented as mean $\pm$ standard
deviation, and categorical data were presented as number
(percentage). The comparative study among the groups was
made by one-way ANOVA following the Bonferroni post hoc
procedure for continuous variables. Fisher’s exact tests
were performed to compare categorical variables between
groups. The association between various baseline
parameters and height increment was identified using
Pearson’s product-moment correlation. To identify the
predictive factors for increase in height, the baseline
parameters that had been significant in former univariate
correlation analyses ($p < 0.05$) were then entered into
a further multiple linear regression analysis. Results of the
regression analysis were presented as unstandardized
regression coefficients ($B$) with their corresponding 95%
confidence intervals and $p$ values.

A value of $p < 0.05$ indicated statistical significance.
Analyses were carried out using SPSS for Windows (SPSS
15.0, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients with GHD

The baseline characteristics of all the patients in the three
groups of GHD are summarized in Table 1. The result of one-
way ANOVA showed that the age at diagnosis of TGDH
was significantly greater than that for IGDH and MPHD
($11.05 \pm 1.85$ vs $8.25 \pm 3.12$ and $8.66 \pm 4.06$ years). Patients
with MPHD had a lower GH peak during the GH provocation
test than did those with IGDH and TGDH ($2.75 \pm 2.31$ vs
$7.65 \pm 2.45$ and $6.63 \pm 2.15$ $\mu$g/L). Patients with MPHD
had a significantly lower SDS for height ($-3.78 \pm 0.84$ vs
$-2.34 \pm 0.61$) and height-target height (Ht-TH) SDS
($-2.96 \pm 1.44$ vs $-1.22 \pm 0.89$) than those with TGDH.
Patients with MPHD had significantly lower SDS for height ($-3.78 \pm 1.44$ vs
$-2.34 \pm 0.61$) and height-target height (Ht-TH) SDS
($-2.96 \pm 1.44$ vs $-1.22 \pm 0.89$) than those with TGDH.
Patients with MPHD had significantly lower IGF-1 levels
($27.74 \pm 25.03$ vs $196.80 \pm 129.76$ ng/mL) and IGF-1 SDS
($-2.45 \pm 0.84$ vs $-0.76 \pm 1.47$) than the TGDH group. The
difference in the gender ratio was found to be significant
($p = 0.021$), the percentage of males being highest for
TGDH (87%) and lowest for MPHD (50%).

Patients in the MPHD group had a comparatively higher
incidence of pituitary hypoplasia ($n = 10$, 83%), pituitary
stalk dysgenesis ($n = 6$, 50%; three subjects showed
absence of a stalk, two had a thin stalk, and one had an
interrupted stalk), and posterior lobe dysgenesis ($n = 6$,
50%; five subjects had an ectopic posterior lobe and one

![Flowchart showing the results of the growth hormone (GH) test expressed in the transient growth hormone deficiency (TGDH), isolated growth hormone deficiency (IGHD; <10 $\mu$g/L), and multiple pituitary hormone deficiency (MPHD; <10 $\mu$g/L accompanied by one or more anterior pituitary hormone deficits) groups before and approximately 6 months after GH treatment.](image-url)

Figure 1
had an absent posterior lobe) when compared to the other two groups. The percentage of other anomalies between the three groups was not significantly different. (Table 1).

**Effect of GH therapy**

The changes in height velocity and height SDS for each individual group from the commencement to the third year of GH treatment is shown in Fig. 2. In each group, the initial response to GH therapy was a vigorous rise in the growth rate, followed by a gradual decline and then stabilization. In all groups, the mean height SDS improved with therapy, the increment ranging from 0.67 to 1.98 SDS.

Longitudinal data on the characteristics and parameters of response during the first 2 years of GH therapy are shown in Table 2. The values, including age, height velocity, height SDS, Ht-TH SDS, body mass index (BMI) SDS, BA, BA-CA, IGF-1, and IGF-1 SDS, were recorded annually during GH treatment. The MPHD group had a significantly higher height velocity in the first year than the TGHD group (9.99 ± 2.75 vs 7.61 ± 1.46 cm/y). After 1 year of GH treatment, there was no significant difference in BMI SDS, BA-CA, IGF-1 level, and IGF-1 SDS among the three groups. The MPHD group had a significantly lower value for Ht SDS (−2.86 ± 1.28 vs −2.05 ± 0.72 SDS) and Ht-TH SDS (−2.04 ± 1.26 vs −0.94 ± 0.94 SDS) than the TGHD group. In addition, the TGHD group had a greater BA than the IGHD and MPHD groups (9.97 ± 2.31, 6.50 ± 4.10, and 7.12 ± 3.40 years, respectively).

A total of 26, 6, and 12 subjects received 2-year GH therapy in the TGHD, IGHD, and MPHD groups, respectively. There was no significant difference in height velocity, height SDS, Ht-TH SDS, BMI SDS, IGDF-1 level, and IGF-1 SDS among three groups after the second year of GH treatment. The MPHD group had a significant BA delay (BA-CA −3.22 ± 2.43 vs −1.13 ± 1.40 years) compared to the TGHD group in the second year. In addition, the TGHD group had a greater BA than the IGHD and MPHD groups (11.83 ± 2.53, 7.46 ± 4.64, and 8.31 ± 3.67 years, respectively).

**Adverse effects during GH treatment**

Two patients complained of pain in their extremities, cramps, or soreness during GH treatment. Two patients had complaints of headache. One patient had mild scoliosis. One patient developed a smooth muscle tumor of uncertain malignant potential on the right thigh after 1 year of GH treatment, and GH was stopped for 1 year. The patient restarted GH treatment 1 year after operation, and the GH treatment was continued for 3 years. So far, this patient has had no recurrence of his smooth muscle tumor.

**Correlation and regression analysis**

Correlations between height increment and various baseline parameters in all patients with GHD after 1 and 2 years of

---

### Table 1 Baseline characteristics of all patients with growth hormone deficiency.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 51)</th>
<th>TGHD (31)</th>
<th>IGHD (8)</th>
<th>MPHD (12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>38 (75)</td>
<td>27 (87)</td>
<td>5 (63)</td>
<td>6 (50)</td>
<td>0.021</td>
</tr>
<tr>
<td>Age of diagnosis (CA) (y)</td>
<td>51</td>
<td>11.05 ± 1.85</td>
<td>8.25 ± 3.12</td>
<td>8.66 ± 4.06</td>
<td>0.007</td>
</tr>
<tr>
<td>Peak GH (µg/L)</td>
<td>51</td>
<td>6.63 ± 2.15</td>
<td>7.65 ± 2.45</td>
<td>2.75 ± 2.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TH SDS</td>
<td>51</td>
<td>−1.12 ± 0.74</td>
<td>−0.96 ± 0.34</td>
<td>−0.82 ± 0.80</td>
<td>0.463</td>
</tr>
<tr>
<td>Puberty (%)</td>
<td>6 (12)</td>
<td>3 (10)</td>
<td>2 (25)</td>
<td>1 (8)</td>
<td>0.472</td>
</tr>
<tr>
<td>Age at start (y)</td>
<td>51</td>
<td>11.37 ± 1.81</td>
<td>8.51 ± 3.08</td>
<td>9.81 ± 4.12</td>
<td>0.021</td>
</tr>
<tr>
<td>HV (cm/y)</td>
<td>51</td>
<td>4.12 ± 1.18</td>
<td>4.21 ± 1.55</td>
<td>3.54 ± 1.23</td>
<td>0.348</td>
</tr>
<tr>
<td>Ht SDS</td>
<td>51</td>
<td>−2.34 ± 0.61</td>
<td>−2.78 ± 0.82</td>
<td>−3.78 ± 1.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ht-TH SDS</td>
<td>51</td>
<td>−1.22 ± 0.89</td>
<td>−1.82 ± 0.66</td>
<td>−2.96 ± 1.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>51</td>
<td>−0.33 ± 0.92</td>
<td>0.17 ± 1.07</td>
<td>−0.12 ± 0.88</td>
<td>0.373</td>
</tr>
<tr>
<td>BA (y)</td>
<td>51</td>
<td>8.19 ± 1.89</td>
<td>5.47 ± 3.77</td>
<td>5.60 ± 2.86</td>
<td>0.002</td>
</tr>
<tr>
<td>BA-CA (y)</td>
<td>51</td>
<td>−2.96 ± 0.96</td>
<td>−2.79 ± 1.77</td>
<td>−4.02 ± 2.26</td>
<td>0.087</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>51</td>
<td>196.80 ± 129.76</td>
<td>134.17 ± 151.88</td>
<td>27.74 ± 25.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>51</td>
<td>−0.76 ± 1.47</td>
<td>−1.34 ± 1.40</td>
<td>−2.45 ± 0.84</td>
<td>0.002</td>
</tr>
<tr>
<td>Brain MRI (%)</td>
<td>50 (98)</td>
<td>31 (100)</td>
<td>7 (88)</td>
<td>12 (100)</td>
<td>0.157</td>
</tr>
<tr>
<td>Pituitary hypoplasia (%)</td>
<td>17 (34)</td>
<td>6 (19)</td>
<td>1 (14)</td>
<td>10 (83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pituitary stalk dysgenesis (%)</td>
<td>7 (14)</td>
<td>0 (0)</td>
<td>1 (14)</td>
<td>6 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior lobe dysgenesis (%)</td>
<td>7 (14)</td>
<td>0 (0)</td>
<td>1 (14)</td>
<td>6 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other anomalies (%)</td>
<td>9 (18)</td>
<td>5 (16)</td>
<td>1 (14)</td>
<td>3 (25)</td>
<td>0.864</td>
</tr>
</tbody>
</table>

Continuous data were presented as mean ± standard deviation, and categorical data were presented as number (percentage). All comparisons of continuous variables among groups were made by one-way ANOVA following the Bonferroni post hoc procedure.

† p < 0.05 vs TGHD.
‡ p < 0.05 vs IGHD.

BA = bone age; BMI = body mass index; CA = chronological age at diagnosis; GH = growth hormone; IGF-1 = insulin-like growth factor; IGHD = isolated growth hormone deficiency; Ht = height; HV = height velocity; MPHD = multiple pituitary hormone deficiency; MRI = magnetic resonance imaging; SDS = standard deviation score; TGHD = transient growth hormone deficiency; TH = target height.
After 1 year of GH treatment (found to be significantly associated with height increments).

Results showed that the pretreatment GH peak value was and entered into a multiple linear regression analysis. Variables that had been significant in the correlation analysis (including pretreatment GH peak, height SDS, Ht-TH SDS, IGF-1, and IGF-1 SDS) were treated as independent variables to predict height increments after 1 and 2 years of GH treatment in patients with GHD. Peak GH has a significantly negative correlation to height increment after 1 and 2 years of GH therapy. Therefore, IGF-1 SDS, rather than IGF-1, could be considered as a diagnostic component for GHD.1,6 The patients with MPHD also had a higher possibility of permanent GHD. Tauber et al17 reported that most (62%) GHD patients have a normal GH test at the end of GH therapy. Similarly, 31 (65%) of 48 patients undergoing re-evaluation of GH secretion after treatment were reassigned to TGHD in our study; a total of 29 (78.4%) of the 37 patients with IGHD had a normal GH response during GH re-evaluation. Only two (18.2%) of the 11 patients with MPHD had normal GH and other hormonal responses when re-evaluated.

On MRI, MPHD patients had a significantly higher frequency of pituitary hypoplasia, pituitary stalk dysgenesis, and ectopic posterior lobe than the other two groups in our study. According to the consensus guidelines of the Growth Hormone Research Society, MRI of the brain with an emphasis on the hypothalamic-pituitary region should be carried out in children finally diagnosed as having GHD.1 MRI of the hypothalamus and pituitary gland can help to clinically evaluate the severity of GHD and the response to GH treatment.6,16

GH therapy was more effective in terms of linear growth in the MPHD group than the IGHD and TGHD groups. The initial response to GH therapy was a vigorous rise in the growth rate, followed by a gradual decline and then stabilization.17 Estimating peak GH before treatment was an important predictive factor for the effect of GH in our patients with GHD. Peak GH has a significantly negative correlation to height increment after 1 and 2 years of GH therapy. GH provocation tests are still very important, rather than IGF-1, could be considered as a diagnostic component for GHD.1,6

Several attempts have been made to define and predict the growth response. In 1981, Frasier et al18 reported a dose–response curve for human GH based on patients’ body weight. Dose-responsiveness has also been considered in more recent studies using higher GH dosages and measures of pubertal status.19–21 No uniform response of

**Table 4** shows the predictive factors for height increments after 1 and 2 years of GH treatment in patients with GHD. The variables that had been significant in the correlation analysis (including pretreatment GH peak, IGF-1 SDS, height SDS, BA-CA, and Ht-TH SDS) were treated as independent variables to predict height increments after 2 years of GH treatment. Pretreatment height SDS was the only independently predictive factor ($B = -0.34$, $p = 0.048$).

**Discussion**

The study reveals that the patients with MPHD represented the most severe form of GHD and had lower peak GH, pretreatment height SDS, Ht-TH SDS, IGF-1, and IGF-1 SDS, as well as greater BA retardation, than the other two groups. There was no significant difference observed between TGHD and IGHD in terms of peak GH, height velocity, height SDS, Ht-TH SDS, BA-CA, IGF-1, and IGF-1 SDS.

The diagnosis of GHD during childhood and adolescence is still controversial,1 and no gold standard has so far existed for the diagnosis of GHD.15 This is related to the coherence between severe GHD and normality, marked variability in GH assays, arbitrary “cut-offs” used to define GHD from GH stimulation tests, and the lack of reproducibility of GH stimulation tests.19 Other tests for the integrity of the GH axis, such as for IGF-1 and IGF binding protein-3, have been therefore considered as a diagnostic component for GHD.1,6 The patients with MPHD also had a higher possibility of permanent GHD. Tauber et al17 reported that most (62%) GHD patients have a normal GH test at the end of GH therapy. Similarly, 31 (65%) of 48 patients undergoing re-evaluation of GH secretion after treatment were reassigned to TGHD in our study; a total of 29 (78.4%) of the 37 patients with IGHD had a normal GH response during GH re-evaluation. Only two (18.2%) of the 11 patients with MPHD had normal GH and other hormonal responses when re-evaluated.

On MRI, MPHD patients had a significantly higher frequency of pituitary hypoplasia, pituitary stalk dysgenesis, and ectopic posterior lobe than the other two groups in our study. According to the consensus guidelines of the Growth Hormone Research Society, MRI of the brain with an emphasis on the hypothalamic-pituitary region should be carried out in children finally diagnosed as having GHD.1 MRI of the hypothalamus and pituitary gland can help to clinically evaluate the severity of GHD and the response to GH treatment.6,16

GH therapy was more effective in terms of linear growth in the MPHD group than the IGHD and TGHD groups. The initial response to GH therapy was a vigorous rise in the growth rate, followed by a gradual decline and then stabilization.17 Estimating peak GH before treatment was an important predictive factor for the effect of GH in our patients with GHD. Peak GH has a significantly negative correlation to height increment after 1 and 2 years of GH therapy. GH provocation tests are still very important, although there are a large number of TGHD and false-positive results.17

IGF-1 level before treatment was not a significant predictive factor for the effect of the first 2 years of GH therapy in this study. However, IGF-1 SDS before treatment had a significant negative correlation with height increment only after 2 years of GH therapy. Therefore, IGF-1 SDS, rather than IGF-1, could be considered as a diagnostic component for GHD.1,6

Several attempts have been made to define and predict the growth response. In 1981, Frasier et al18 reported a dose–response curve for human GH based on patients’ body weight. Dose-responsiveness has also been considered in more recent studies using higher GH dosages and measures of pubertal status.19–21 No uniform response of
Table 2: Longitudinal data on the characteristics and parameters of response during the first two years of growth hormone therapy.

<table>
<thead>
<tr>
<th>Year/characteristics</th>
<th>Total</th>
<th>Patient group</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TGHD (31)</td>
<td>IGHD (8)</td>
<td>MPHD (12)</td>
</tr>
<tr>
<td>First year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>51</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51</td>
<td>12.36 ± 1.79</td>
<td>9.46 ± 3.06†</td>
</tr>
<tr>
<td>HV (cm/y)</td>
<td>51</td>
<td>7.61 ± 1.46†</td>
<td>8.14 ± 1.92</td>
</tr>
<tr>
<td>Ht SDS</td>
<td>51</td>
<td>−2.05 ± 0.72</td>
<td>−2.23 ± 0.76</td>
</tr>
<tr>
<td>Ht-TH SDS</td>
<td>51</td>
<td>−0.94 ± 0.94</td>
<td>−1.27 ± 0.73</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>51</td>
<td>−0.30 ± 0.84</td>
<td>0.001 ± 1.07</td>
</tr>
<tr>
<td>BA (y)</td>
<td>50</td>
<td>9.97 ± 2.31</td>
<td>6.50 ± 4.10†</td>
</tr>
<tr>
<td>BA-CA (y)</td>
<td>50</td>
<td>−2.23 ± 1.21</td>
<td>−2.72 ± 1.98</td>
</tr>
<tr>
<td>IGF-1</td>
<td>34</td>
<td>352.60 ± 172.84</td>
<td>194.08 ± 128.45</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>34</td>
<td>−0.21 ± 2.16</td>
<td>−0.73 ± 1.36</td>
</tr>
<tr>
<td>Second year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>44</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Age (y)</td>
<td>44</td>
<td>13.29 ± 1.78</td>
<td>9.76 ± 3.25†</td>
</tr>
<tr>
<td>HV (cm/y)</td>
<td>44</td>
<td>7.85 ± 1.95</td>
<td>5.97 ± 1.22</td>
</tr>
<tr>
<td>Ht SDS</td>
<td>44</td>
<td>−1.71 ± 0.69</td>
<td>−2.06 ± 0.89</td>
</tr>
<tr>
<td>Ht-TH SDS</td>
<td>44</td>
<td>−0.98 ± 1.03</td>
<td>−1.09 ± 0.71</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>44</td>
<td>−0.38 ± 0.92</td>
<td>−0.11 ± 0.83</td>
</tr>
<tr>
<td>BA (y)</td>
<td>44</td>
<td>11.83 ± 2.53</td>
<td>7.46 ± 4.64†</td>
</tr>
<tr>
<td>BA-CA (y)</td>
<td>44</td>
<td>−1.13 ± 1.40</td>
<td>−1.90 ± 1.69</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>22</td>
<td>392.00 ± 202.28</td>
<td>139.33 ± 31.66</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>22</td>
<td>−0.55 ± 1.43</td>
<td>−0.89 ± 0.68</td>
</tr>
</tbody>
</table>

Data were presented as mean ± standard deviation. All comparisons among groups were made by one-way ANOVA following the Bonferroni post hoc procedure.

† p < 0.05 vs TGHD.
§ p < 0.05 vs MPHD.

BA = bone age; BMI = body mass index; CA = chronological age at diagnosis; IGF-1 = insulin-like growth factor; IGHD = isolated growth hormone deficiency; Ht = height; HV = height velocity; MPHD = multiple pituitary hormone deficiency; SDS = standard deviation score; TGHD = transient growth hormone deficiency; TH = target height.

Table 3: Correlations between height increment and various baseline parameters in all patients with growth hormone deficiency after 1 and 2 years of treatment with growth hormone.

<table>
<thead>
<tr>
<th>Pretreatment variables</th>
<th>ΔHt SD score 0–1 y</th>
<th>ΔHt SD score 0–2 y</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak GH</td>
<td>51</td>
<td>−0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF-1</td>
<td>50</td>
<td>−0.23</td>
<td>0.110</td>
</tr>
<tr>
<td>IGF-1 SDS</td>
<td>50</td>
<td>−0.16</td>
<td>0.258</td>
</tr>
<tr>
<td>Height SDS</td>
<td>51</td>
<td>−0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BA-CA (y)</td>
<td>51</td>
<td>−0.25</td>
<td>0.081</td>
</tr>
<tr>
<td>Age at start (y)</td>
<td>51</td>
<td>−0.17</td>
<td>0.220</td>
</tr>
<tr>
<td>Ht-TH SDS</td>
<td>51</td>
<td>−0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TH SDS</td>
<td>51</td>
<td>0.12</td>
<td>0.411</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short-term variables</th>
<th>ΔIGF-1</th>
<th>p</th>
<th>ΔSDS 0–1 y</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>34</td>
<td>0.21</td>
<td>0.230</td>
<td>0.04</td>
</tr>
</tbody>
</table>

BA = bone age; CA = chronological age at diagnosis; GH = growth hormone; IGF-1 = insulin-like growth factor; Ht = height; SDS = standard deviation score; TH = target height.

In addition to dose–response models and reports, various models of prediction have been established. In 1993, Blethen et al reported that chronological age, log of maximum GH response, weight (adjusted for height), log of GH dose, and mid-paternal height could predict the response to the first year of GH treatment. In 1997, Kristrom et al reported that IGF-1 SDS, log of maximum GH response, initial age, weight SDS at 1 year of age, and short-term change in IGF-1 SDS could explain 58% of the variation in GH response.

Ranke et al in 1999 analyzed the Kabi Pharmacia International Growth Study data and reported that the variables for the first-year growth response were the natural log of the maximum GH response, chronological age, Ht-TH SDS, body weight SDS, GH dose, and birthweight SDS. Four predictors for the second-, third-, and fourth-year growth responses were height velocity during the previous year (positively correlated), body weight SDS (positively correlated), chronological age (negatively correlated), and natural log of weekly GH dose (positively correlated). Chen et al in 2001 analyzed 23 Taiwanese patients undergoing GH treatment and reported that their response to a given dose of GH has been seen. In 2010, Cohen et al developed a new GH dosing algorithm based on patients’ IGF-1 responses.
final height was correlated to the initial height SDS, TH SDS, predicted height by the BA at the beginning of treatment, and height SDS at the onset of puberty.

In the current study, the dosage of GH given to our patients with GHD was low and fixed at 0.48 IU/kg/wk (0.16 mg/kg/d) according to the policy of the Bureau of National Health Insurance in Taiwan. In spite of a low dose of GH therapy, we observed that change in height SDS in the first year had a significant negative correlation with the following variables: peak GH, pretreatment height SDS, and Ht-TH SDS. The change in height SDS in the first 2 years had a significant negative correlation with peak GH, IGF-1 SDS, height SDS, BA-CA, and Ht-TH SDS. The significant correlation with change in height SDS in the first 3 years was similar to changes in the first 2 years. After using multiple linear regressions, pretreatment GH peak value was shown

![Figure 3](image-url)  

**Figure 3** Individual values for parameters (peak growth hormone, height SDS, Ht-TH SDS) at the start of growth hormone treatment plotted against individual 1-year and 2-year growth responses, expressed as height SDS. Ht-TH = height-target height; SDS = standard deviation score.
to be the predicting factor for height increments after 1 year of GH treatment. The predicting factor for height increments after 2 years of GH treatment was height SDS.

The mainstay of MPHD is replacement with the appropriate hormones. Thyroxine should be given if serum free or total thyroxine level is low. Growth should be meticulously monitored, and if height velocity is poor and GHD is confirmed by stimulation tests, GH treatment should be given until linear growth ceases. Sex steroids such as estrogen or testosterone should be commenced at puberty if gonadotropin deficiency is confirmed.26

Our study had many limitations, such as inadequate sample size and three (6%) of the 51 patients the patients not receiving GH re-evaluation after completion of GH treatment. However, these three patients belong to MPHD group, and only two (18%) of the 11 patients with MPHD were reassigned to the TGHD group after re-testing of GH.

In conclusion, the administration of GH to children with GHD results in a pronounced acceleration of linear growth, mostly during the first year of treatment, particularly in MPHD group. The diagnosis of GHD requires comprehensive auxological, biochemical (GH provocation test, IGF-1, and IGF-binding protein-3), and brain MRI assessment. We suggestively conclude that the patients with GHD, especially IGHD, must undergo re-evaluation of GH secretion after completion of GH therapy.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfma.2011.06.011.

References


