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Effect of Growth Hormone (GH) Treatment on the Near-Final Height of 1258 Patients with Idiopathic GH Deficiency: Analysis of a Large International Database

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Context: Treatment with GH has been used to correct the growth deficit in children with GH deficiency (GHD). Although successful in increasing height velocity, such treatment often falls short of helping patients achieve full genetic height potential.

Objective: This study set out to analyze near-final height (FH) data from a cohort of GH-treated children with idiopathic GHD.

Design, Setting, and Participants: Of 1258 evaluable patients in the Pfizer International Growth Database (KIGS) with GHD, 980 were of Caucasian origin, and 278 were of Japanese origin; 747 had isolated GHD (IGHD), and 511 had multiple pituitary hormone deficiencies (MPHD).

Main Outcome Measures: Near-FH, relation to midparental height, and factors predictive of growth outcomes were the main outcome measures.

Results: Median height SD scores (SDS) at the start of treatment were −2.4 (IGHD) and −2.9 (MPHD) for Caucasian males and −2.6 (IGHD) and −3.4 (MPHD) for females, respectively; comparable starting heights were −2.9 (IGHD) and −3.6 (MPHD) for Japanese males and −3.3 (IGHD) and −4.0 (MPHD) for females, respectively. Corresponding near-adult height SDS after GH treatment were −0.8 (IGHD) and −0.7 (MPHD) for Caucasian males and −1.0 (IGHD) and −1.1 (MPHD) for females, respectively; and −1.6 (IGHD) and −1.9 (MPHD) for Japanese males and −2.1 (IGHD) and −1.8 (MPHD) for females, respectively. Differences between near-adult height and midparental height ranged between −0.6 and +0.2 SDS for the various groups, with the closest approximation to MPH occurring in Japanese males with MPHD. The first-year increase in height SDS and prepubertal height gain was highly correlated with total height gain, confirming the importance of treatment before pubertal onset.

Conclusions: It is possible to achieve FH within the midparental height range in patients with idiopathic GHD treated from an early age with GH, but absolute height outcomes remain in the lower part of the normal range. Patients with MPHD generally had a slightly better long-term height outcome. **(*J Clin Endocrinol Metab* 91: 2047–2054, 2006)**

MORE THAN 1400 patients with GH deficiency (GHD) treated predominantly with biosynthetic GH (1–11) have reached an actual or near-final adult height SD score (SDS) approximately −1.3 SD below the mean. These results include data from the two largest surveys of the efficacy and safety of GH treatment in children (9–11). Despite the availability for therapy of GH that is unlimited by production capacity, long-term studies show that most patients still fail to reach their genetic midparental target heights. The mean adult height in 121 patients treated in Genentech GH trials was −0.7 SDS, with 106 being within 2 SDS of the normal adult height of Americans (4). Even in these closely followed patients, a −0.4 to −0.6 SDS difference from their midparental height occurred. Achieving an individual's genetic midparental target height, however, is possible. A Swedish group of very closely monitored patients treated with conventional European doses (lower than those used in the United States) nonetheless reached a median final height (FH) SDS of −0.32, which was equivalent to their midparental height (11). Although the development of recombinant GH has minimized the problem of supply experienced in the era of treatment with pituitary GH, delays in both diagnosis and initiation of therapy continue to compromise adult height.

This report is the most recent assessment of near-adult height in the large group of patients with idiopathic GHD, of both the isolated (IGHD) and multiple pituitary hormone deficiency (MPHD) varieties, who have been followed in the Pfizer International Growth Database (KIGS). Our objective was to determine whether the trend toward uninterrupted GH treatment from a younger age has yielded more successful long-term height outcomes.

Subjects and Methods

The KIGS database is an international registry developed with the main objective of documenting the long-term outcomes and safety of Somatonorm and Genotropin GH products (Pfizer, Inc., New York, NY). The KIGS survey was performed in accordance with the recommendations adopted by the 18th World Medical Assembly (held in Helsinki, Finland, in 1964) and any subsequent revisions, which exist to guide physicians carrying out biomedical research involving human individuals. Each subject and/or his/her legal representative received adequate information, had the right to withdraw from the survey at any time, and consented to his/her participation. In contrast, this kind of registry or

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Abbreviations: FH, Final height; GHD, GH deficiency; IGHD, isolated GHD; MPHD, multiple pituitary hormone deficiencies; SDS, SD score.

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noninterventional trial that KIGS represents did not require informed consent from the subjects or legally acceptable representatives in many countries during the first decade of its existence. Currently, informed consent is required and conforms to allow anonymous use of the data in compliance with rigorous privacy guidelines.

Data from patients enrolled in the KIGS registry were reviewed for this analysis. In total, 53,736 patients from 48 countries were enrolled in the database as of January 9, 2005, with 25,178 having idiopathic GHD. It should be noted that there are few patients (n = 31) from the United States in this report of final adult height (Fig. 1). GH produced by Pfizer has not been available in the United States for a sufficiently long period to generate a substantial number of patients attaining final adult height. All patients in the analysis were treated with recombinant human GH (Genotropin, Pfizer, New York, NY). The diagnosis of idiopathic GHD was made by the individual KIGS investigator according to the KIGS etiology Classification List (no. 1.1) and was based on a maximum GH concentration of less than 10 ng/ml in two standard stimulation tests. Of these patients with idiopathic GHD, 1,258 were defined as having achieved their near-adult height. For the purposes of this assessment, patients were considered to have reached near-adult height when height velocity was less than 2 cm/yr, as calculated over a period of more than 9 months, chronological age was more than 17 yr in boys and more than 15 yr in girls, or skeletal age was more than 16 yr in boys and more than 14 yr in girls. GH therapy was given for at least 4 yr and included at least 1 yr of prepubertal treatment. Midparental height (height adjusted for gender) was calculated and expressed in terms of SDS, as described by Ranke (12). Reference growth data for Japanese children were obtained from Suwa and Tachibana (13). The long-term response to GH was evaluated by three different, but complementary, methods: first, the actual height expressed as a height SDS; second, the gain in height SDS, calculated as the near-adult height SDS minus the initial height SDS; and third, height relative to midparental height, calculated as near-adult height SDS minus midparental height SDS. Sixty percent of the children with idiopathic GHD had IGHD. The remainder of the patients had gonadotropin deficiency, with or without TSH and/or ACTH deficiencies.

Statistics

Wilcoxon rank tests were used for comparisons of outcome measures. Median values, 10–90th percentiles, and Pearson correlation coefficients are presented; *P* values correspond to two-sided tests. Mean and SD values are given where appropriate. The procedure REG in the program package SAS, version 8 (SAS Institute, Cary, NC), was used for multivariate regression analyses.

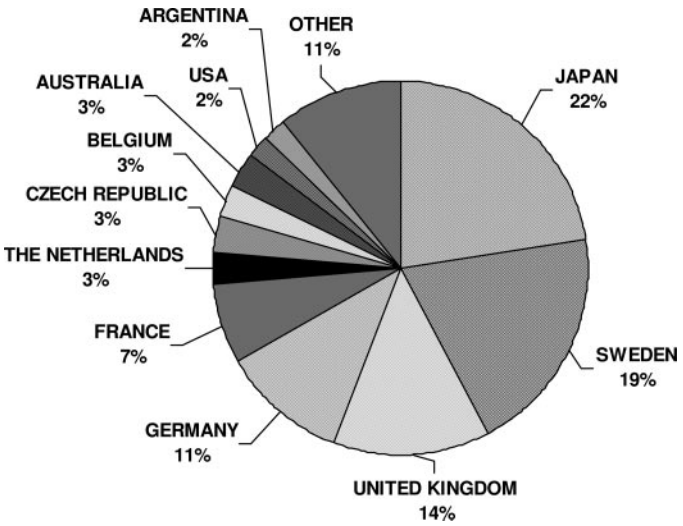

FIG. 1. The percent contributions of countries from around the world, which make up the near-adult height database for GH-treated patients with idiopathic GHD.

Results

Pretreatment auxology and demography

The pretreatment characteristics of patients with IGHD who reached near-adult height are shown in Table 1, with data from Caucasian and Japanese patients as well as those with IGHD or MPHD given separately. Kruskal-Wallis analysis revealed significant ($P < 0.05$) differences between the populations for all variables listed, except birth weight. Of the 1258 patients (980 of Caucasian origin and 278 of Japanese origin), 37% were females; 60% had isolated IGHD and thus underwent spontaneous puberty. The median initial GH dose was approximately 0.2 mg/kg·wk in the Caucasian children and about 0.18 mg/kg·wk in the Japanese children. In both sexes, GH treatment was initiated at a significantly younger age in the Caucasian children than in the Japanese children ($P < 0.001$), whereas females in both groups started GH at a younger age than males ($P < 0.001$). Furthermore, the patients with MPHD started GH at a younger age than those with IGHD ($P < 0.001$).

The median height SDS ranged from −2.4 in Caucasian males (IGHD) to −4.0 in Japanese females (MPHD; Table 1), with the IGHD children being relatively taller in all groups than the MPHD children. In addition, the patients' parents were relatively short, as indicated by median midparental heights of −0.1 to −0.6 in Caucasian children and −0.7 to −1.6 in Japanese children; the IGHD parents were smaller in each of the groups. The median difference between height SDS and midparental height SDS ranged widely; the distance to midparental height was less in the Japanese children, and the distance to the midparental target was less in IGHD than in MPHD children. Height SDS at baseline differed between sexes in both Caucasian ($P < 0.001$) and Japanese ($P < 0.001$) children; females were shorter than males in both groups, a finding found in both IGHD and MPHD groups.

Effect of GH treatment

The auxological characteristics of the patients with IGHD at near-FH are shown in Table 2 and Figs. 2 and 3. Caucasian children generally had a longer duration of GH therapy than Japanese children due to their younger ($P < 0.001$) age at the start of treatment. More clearly, however, the MPHD group had a longer duration of treatment than the IGHD group by 2–2.5 yr, largely due to earlier initiation of treatment. The GH dose and the frequency of injections were both significantly ($P < 0.001$) lower in the Japanese children. Caucasian IGHD children had higher GH doses and greater frequency of injections than those with MPHD.

The median near-adult height SDS in Caucasian patients in all groups was significantly greater ($P < 0.001$) than that in the Japanese patients, as was the increase in height SDS (Table 2). The near-adult height SDS for females in both groups was lower than that in males in both IGHD and MPHD patients. Japanese males achieved a height closer to their midparental height than did Caucasian males ($P < 0.001$) in both IGHD and MPHD groups, whereas the difference between Caucasian and Japanese females ($P < 0.02$) was more modest. In both ethnic groups, males at near-adult height were closer to their midparental height than females. There was no appreciable increase in height SDS after the

TABLE 1. Pretreatment data for patients with idiopathic IGHD (A) and for patients with idiopathic GHD and MPHD (B), split according to gender and ethnic origin

	Females		Males	
	Caucasian (n = 200)	Japanese (n = 68)	Caucasian (n = 351)	Japanese (n = 128)
A				
Age (yr)	9.3 (4.3 to 11.7)	9.9 (5.2 to 12.3)	10.1 (5.3 to 13.0)	11.7 (6.3 to 14.0)
Birth weight SDS	−0.6 (−2.4 to 0.8)	−0.3 (−1.4 to 0.7)	−0.6 (−1.9 to 0.8)	−0.3 (−1.7 to 0.8)
TH SDS	−0.6 (−1.9 to 1.0)	−1.6 (−2.6 to −0.7)	−0.6 (−1.7 to 1.0)	−1.6 (−2.6 to −0.3)
Height SDS	−2.6 (−3.9 to −1.7)	−3.3 (−5.0 to −2.4)	−2.4 (−3.6 to −1.6)	−2.9 (−4.8 to −2.2)
Height SDS − TH SDS	−2.1 (−4.2 to −0.6)	−0.9 (−2.5 to 0.2)	−1.9 (−3.6 to −0.7)	−0.7 (−2.4 to 0.6)
Weight SDS	−2.3 (−4.1 to −1.0)	−3.0 (−4.4 to −1.2)	−2.1 (−3.9 to −0.7)	−2.5 (−4.4 to −0.9)
Body mass index SDS	−0.5 (−1.8 to 0.7)	−0.9 (−1.9 to 0.6)	−0.3 (−1.7 to 1.2)	−0.3 (−1.8 to 1.1)
Mean GH dose (mg/kg·wk)	0.21 (0.13 to 0.30)	0.18 (0.15 to 0.21)	0.22 (0.13 to 0.30)	0.17 (0.12 to 0.21)
	Females		Males	
	Caucasian (n = 172)	Japanese (n = 26)	Caucasian (n = 257)	Japanese (n = 56)
B				
Age (yr)	7.2 (2.7 to 11.5)	8.4 (3.8 to 12.8)	8.0 (4.0 to 12.9)	9.6 (5.1 to 13.9)
Birth weight SDS	−0.7 (−2.3 to 1.0)	−0.4 (−2.3 to 1.5)	−0.5 (−2.1 to 1.1)	−0.3 (−1.5 to 0.9)
TH SDS	−0.07 (−1.7 to 1.3)	−0.7 (−2.1 to −0.1)	−0.3 (−1.7 to 1.4)	−1.0 (−1.9 to 0.3)
Height SDS	−3.4 (−4.8 to −2.1)	−4.0 (−5.4 to −2.7)	−2.9 (−4.6 to −1.8)	−3.6 (−4.9 to −2.4)
Height SDS − TH SDS	−3.2 (−5.4 to −1.3)	−2.0 (−3.7 to −0.7)	−2.7 (−4.7 to −1.2)	−1.7 (−2.9 to −0.5)
Weight SDS	−3.0 (−5.0 to −1.0)	−3.0 (−6.0 to −1.4)	−2.5 (−4.9 to −0.7)	−2.8 (−4.8 to −1.3)
Body mass index SDS	−0.15 (−2.0 to 1.2)	−0.8 (−2.3 to 1.1)	−0.16 (−1.7 to 1.4)	−0.18 (−2.1 to 1.6)
Mean GH dose (mg/kg·wk)	0.20 (0.13 to 0.34)	0.17 (0.13 to 0.21)	0.19 (0.12 to 0.31)	0.19 (0.12 to 0.28

Values are given as medians, with 10th−90th percentiles in *parentheses*. TH, Midparental height or target height.

start of puberty (data not shown), as reported previously (10–12), and there was no correlation between the height gained during puberty and the total height gained from the initiation of treatment to near-adult height in either IGHD or MPHD.

When we contrasted long-term outcomes of IGHD to MPHD patients, the MPHD children had a more robust outcome ($P < 0.001$) in both near-adult height SDS and maximum change in height SDS. As noted above, however, they were still far from the midparental height, especially in Caucasian subjects.

Extensive analyses were undertaken to determine whether there were any correlations between the total height increment and various baseline parameters. These are shown in Table 3 for univariate analysis and Table 4 for multivariate analysis. Univariate analysis showed that the first-year increase in height SDS (Fig. 4) as well as the prepubertal height gain (Fig. 5) were most highly correlated with the total height gain. Correlations also existed between total height gain and age at onset of GH treatment, maximum GH peak during a standard stimulation test, height at initiation of GH, midparental height, and duration of GH therapy. Multivariate analysis revealed an r^2 value of 0.56 relating the total increase in height to midparental height, height gain in the first year,

TABLE 2. Characteristics of patients with idiopathic IGHD (A) and patients with idiopathic GHD and MPHD (B) at near-FH after treatment with GH

	Females		Males	
	Caucasian (n = 200)	Japanese (n = 68)	Caucasian (n = 351)	Japanese (n = 128)
A				
Age (yr)	16.6 (15.3–18.3)	16.8 (15.5–19.3)	18.2 (17.3–20.0)	18.3 (17.3–20.2)
Duration of GH treatment (yr)	6.9 (4.4–11.7)	7.0 (4.7–10.4)	7.5 (5.3–12.1)	6.7 (4.5–10.3)
Mean GH dose (mg/kg·wk)	0.20 (0.14–0.28)	0.16 (0.13–0.19)	0.22 (0.15–0.29)	0.15 (0.11–0.17)
Mean no. of injections/wk	6.7 (4.8–7.0)	4.8 (2.6–6.5)	6.8 (5.4–7.0)	5.2 (3.0–6.8)
Near-adult height SDS	−1.0 (−2.6 to 0.3)	−2.1 (−3.6 to −1.0)	−0.8 (−2.1 to 0.4)	−1.6 (−3.3 to −0.8)
Increase in height SDS	1.6 (0.4 to 3.1)	0.6 (−0.2 to 1.6)	1.6 (0.5 to 2.8)	0.7 (−0.1 to 2.0)
Height SDS − TH SDS	−0.5 (−2.0 to 0.7)	−0.3 (−1.5 to 1.0)	−0.2 (−1.9 to 1.0)	0.1 (−1.4 to 1.1)
	Females		Males	
	Caucasian (n = 172)	Japanese (n = 26)	Caucasian (n = 257)	Japanese (n = 56)
B				
Age (yr)	17.6 (15.6–19.9)	18.4 (15.6–22.2)	19.0 (17.6–22.0)	19.8 (18.0–23.8)
Mean GH dose (mg/kg·wk)	0.18 (0.14–0.29)	0.17 (0.12–0.19)	0.18 (0.12–0.28)	0.16 (0.12–0.22)
Mean no. of injections/week	6.1 (4.3–7.0)	5.8 (3.4–6.8)	6.1 (4.5–7.0)	4.5 (2.8–6.7)
Near-adult height SDS	−1.1 (−2.7 to 0.7)	−1.8 (−3.5 to −0.3)	−0.7 (−2.3 to 0.9)	−1.3 (−2.8 to 0.1)
Increase in height SDS	2.3 (0.5 to 4.2)	1.6 (−0.5 to 3.3)	2.3 (1.1 to 3.9)	1.9 (0.1 to 3.1)
Height SDS − TH SDS	−0.8 (−2.5 to 0.8)	−0.46 (−2.1 to 0.3)	−0.4 (−2.0 to 0.7)	0.2 (−1.3 to 0.9)

Patients are split according to gender and ethnic origin, and values are given as medians, with 10th–90th percentiles in *parentheses*. TH, Midparental or target height.

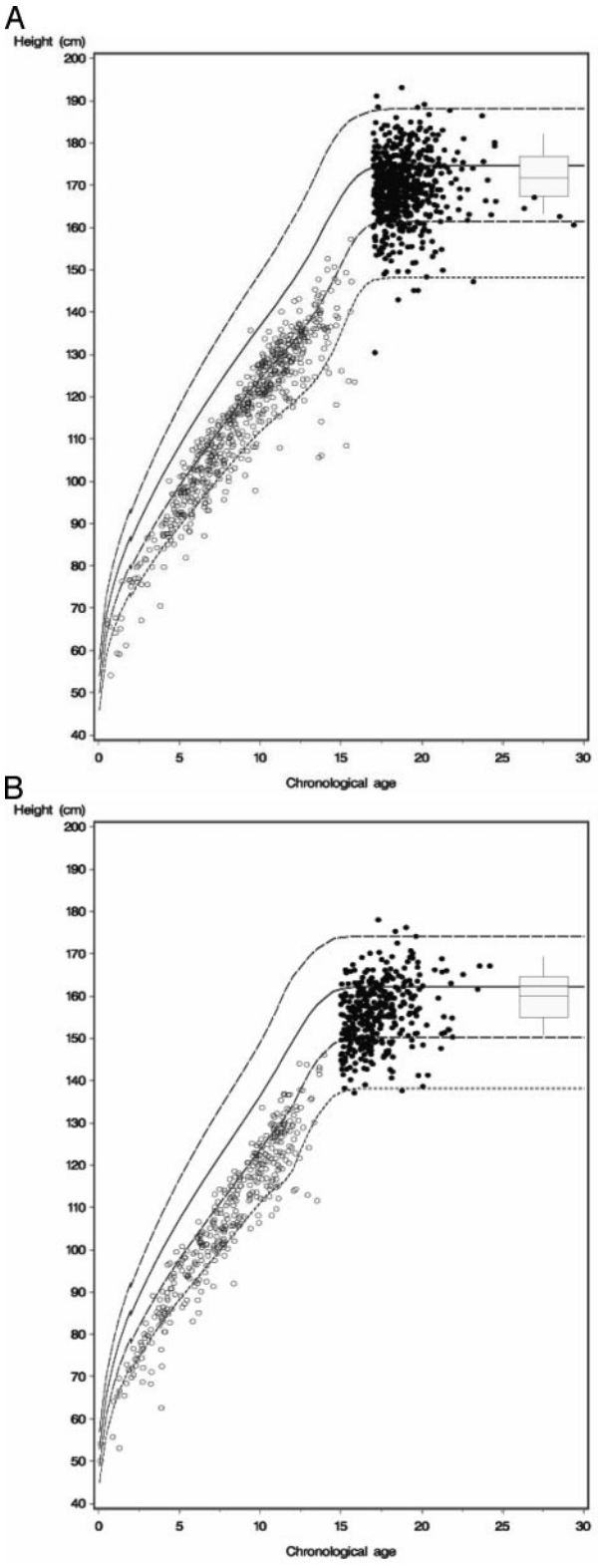

FIG. 2. Starting height (○) and near-adult height (●) after GH treatment in male (A; n = 505) and female (B; n = 331) Caucasian children with idiopathic GHD. The curves represent means (*solid lines*), ±2 SD (*broken lines*), and −4 SD (*dotted lines*). *Box plots* represent medians and 25th and 75th percentiles, with *whiskers* at the 10th and 90th percentiles.

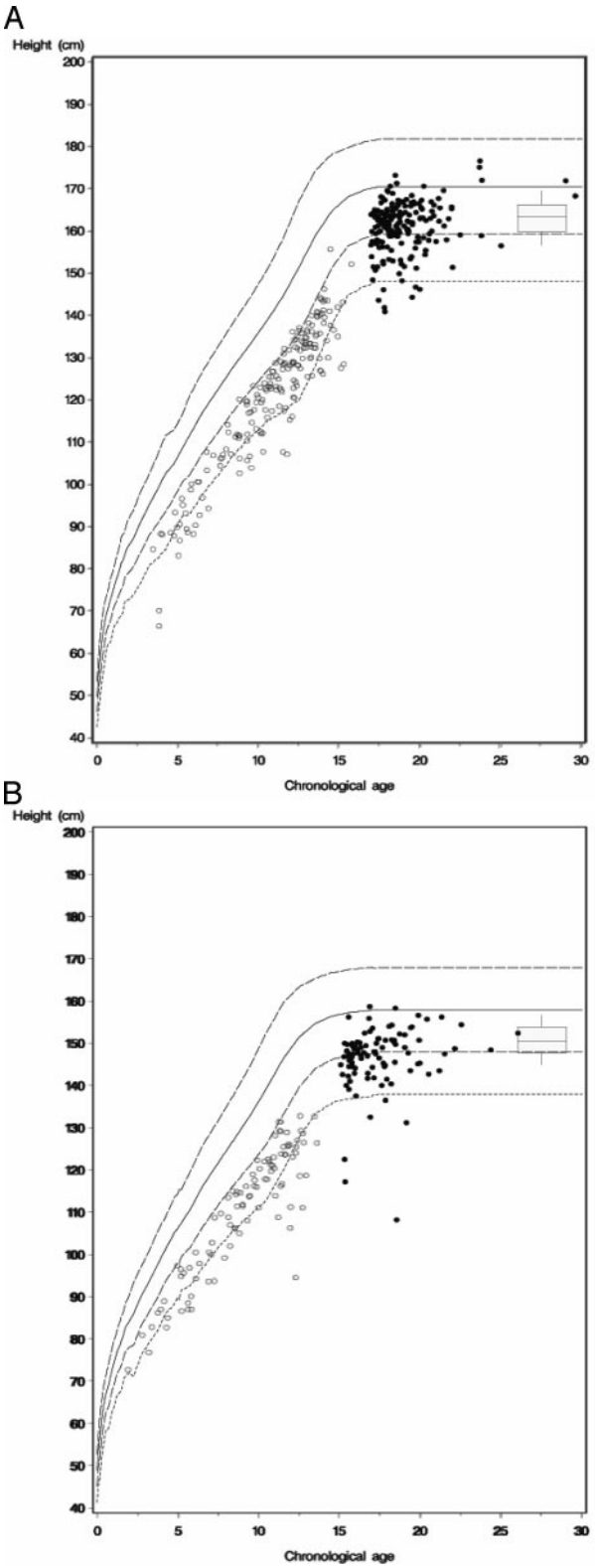

FIG. 3. Starting height (○) and near-adult height (●) after GH treatment in male (A; n = 198) and female (B; n = 98) Japanese children with idiopathic GHD. The curves represent means (*solid lines*), ±2 SD (*broken lines*), and −4 SD (*dotted lines*). *Box plots* represent medians and 25th and 75th percentiles, with *whiskers* at the 10th and 90th percentiles.

TABLE 3. Univariate correlations between the total height increment and various baseline parameters in GH-treated children with idiopathic GHD (IGHD and MPHD; A), GH-treated children with idiopathic IGHD (B), and GH-treated children with idiopathic GHD and MPHD (C)

	n	Pearson correlation coefficient	*P*
A			
Starting height SDS	1270	−0.37	<0.0001
Duration of GH treatment (yr)	1270	0.48	<0.0001
Age (yr)	1270	−0.37	<0.0001
Maximum GH peak (ng/ml)	1270	−0.48	<0.0001
Birth weight SDS	1183	0.10	<0.0005
Midparental height SDS	1199	0.42	<0.0001
IGHD (% of patients)	1258	−0.33	<<.0001
First-year change in height SDS	1123	0.58	<0.0001
Prepubertal change in height SDS	465	0.75	<0.0001
GH dose at start (mg/kg·wk)	1270	0.25	<0.0001
Mean GH dose	1270	0.08	<0.0032
B			
Starting height SDS	747	−0.18	<0.0001
Duration of GH treatment (yr)	747	0.41	<0.0001
Age (yr)	747	−0.32	<0.0001
Maximum GH peak (ng/ml)	747	−0.38	<0.0001
Birth weight SDS	690	0.12	<0.0013
Midparental height SDS	709	0.44	<0.0001
First-year change in height SDS	667	0.58	<0.0001
Prepubertal change in height SDS	245	0.69	<0.0001
GH dose at start (mg/kg·wk)	747	0.30	<0.0001
Mean GH dose	747	0.18	<0.0001
C			
Starting height SDS	511	−0.43	<0.0001
Duration of GH treatment (yr)	511	0.43	<0.0001
Age (yr)	511	−0.32	<0.0001
Maximum GH peak (ng/ml)	511	−0.43	<0.0001
Birth weight SDS	483	0.10	<0.02
Midparental height SDS	480	0.33	<0.0001
First-year change in height SDS	445	0.52	<0.0001
Prepubertal change in height SDS	218	0.77	<0.0001
GH dose at start (mg/kg·wk)	511	0.20	<0.0001
Mean GH dose	511	0.02	0.67

height at the start of GH therapy, duration of GH treatment, the maximum GH peak during a stimulation test, presence or absence of MPHD, and birth weight. The presence or absence of MPHD was not a significant variable in the model ($P = 0.1232$). The most influential variables with high positive correlations were the midparental height SDS and the first-year growth response.

Discussion

Studies reporting the FH outcomes of patients with IGHD have usually involved rather modest numbers, and results have generally been somewhat disappointing (1–11). In the present study we analyzed data from 1258 GH-treated patients who had reached near-adult height to determine which factors may affect the attainment of normal stature in adulthood. The results show that Caucasian patients with IGHD treated with GH achieved a near-adult height of −0.8 and −1.0 SDS in males and females, respectively; in patients with MPHD, the near-adult heights were −0.7 and −1.1 SDS in males and females, respectively. Japanese patients with IGHD, in contrast, achieved a much lower near-adult height (−1.6 SDS in males and −2.1 SDS in females), although it was still within the normal range for the population. The MPHD

TABLE 4. Mulivariate analysis of correlations between the total height increment (Ht SDS) and various baseline parameters in 1258 GH-treated children with idiopathic GHD (both isolated and MPHD; A), 604 GH-treated children with idiopathic IGHD (B), and 405 GH-treated children with idiopathic GHD and MPHD (C)

	Spearman partial correlation coefficient	*P*
A		
Starting height SDS	−0.22	<0.0001
Maximum GH peak (ng/ml)	−0.21	<0.0001
Birth weight SDS	0.07	<0.02
Midparental height SDS	0.36	<0.0001
Multiple deficiencies (% of patients)	−0.06	<0.07
First-year change in height SDS	0.31	<0.0001
Duration of GH treatment (yr)	0.14	<0.0001
B		
Starting height SDS	−0.16	<0.0001
Maximum GH peak (ng/ml)	−0.17	<0.0001
Birth weight SDS	0.07	<0.07
Midparental height SDS	0.41	<0.0001
First-year change in height SDS	0.36	<0.0001
Duration of GH treatment (yr)	0.11	<0.01
C		
Starting height SDS	−0.34	<0.0001
Maximum GH peak (ng/ml)	−0.22	<0.0001
Birth weight SDS	0.06	0.20
Midparental height SDS	0.29	<0.0001
First-year change in height SDS	0.25	<0.0001
Duration of GH treatment (yr)	0.18	<0.0003

patients reached heights of −1.3 and −1.8 SDS for males and females. As shown previously (14), patients with gonadotropin deficiency generally have a slightly better adult height outcome than those with endogenous presence of normal sex steroid levels. Nonetheless, these current outcome data remain somewhat disappointing and stress the necessity of earlier diagnosis and optimization of treatment of individual patients.

The difference between near-adult height SDS and midparental target height SDS is perhaps the best indication of whether an individual has achieved his/her genetic height potential. This difference was −0.2 to −0.4 in male and −0.4 to −0.5 in female Caucasian patients and was +0.1 to +0.2 in male and −0.3 to −0.6 in female Japanese patients. Both ethnic groups, therefore, appear to have achieved a height close to their genetic potential. In the Japanese patients, however, interpretation of the data was complicated by the current secular trend in height of the Japanese population, with parental heights not necessarily representing the true genetic potential of the present generation (15, 16).

For the Caucasian patients in this study (n = 980), the near-adult height outcomes were slightly better than those reported 5 yr previously from the KIGS database (n = 269; FH, −0.9 to −1.2 SDS, male to female) (10, 11) and from the National Cooperative Growth Study in the United States (n = 258; FH, −1.3 to − 1.9, male to female) (9). The present results for the European patients, however, are generally similar to those for GH-treated children reported from early Genentech trials (n = 121; FH, −0.7, male and female) (4) and for Belgian children (n = 61; FH, −0.8, male and female) reported by Thomas *et al.* (17). In these children with GHD, however, near-adult height remained below the midparental height (17), suggesting a failure to achieve full genetic height po-

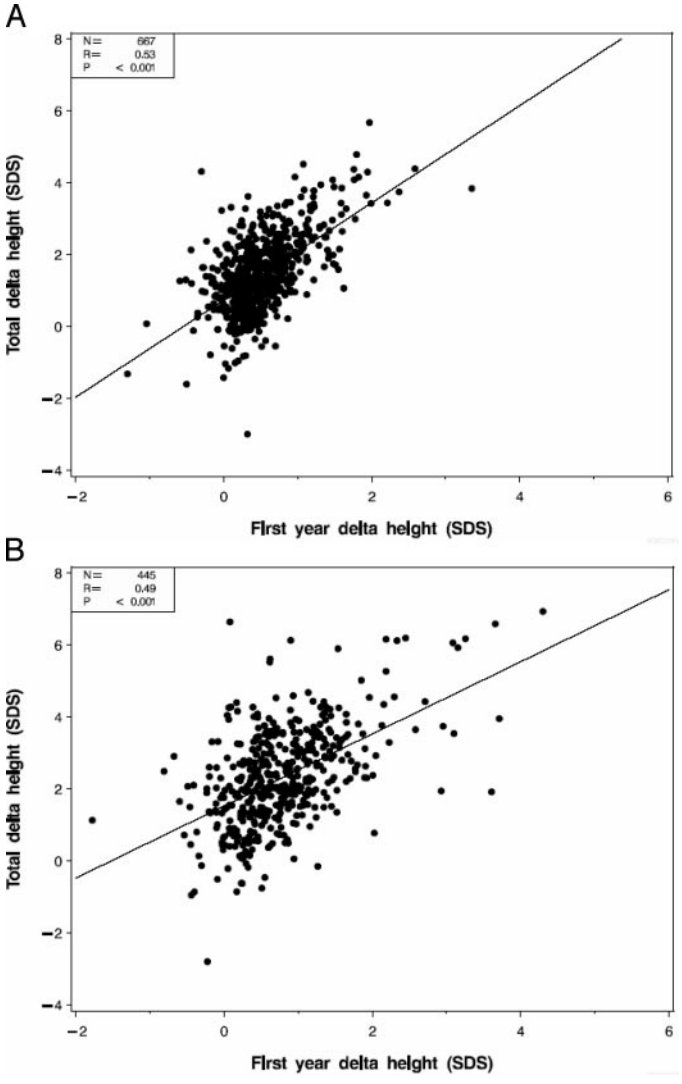

FIG. 4. Relationship between first-year change in height SDS (Δ SDS) and total change in height SDS between the start of GH treatment and near-FH in children with idiopathic GHD. A, Data in children with IGHD; B, data in children with MPHD.

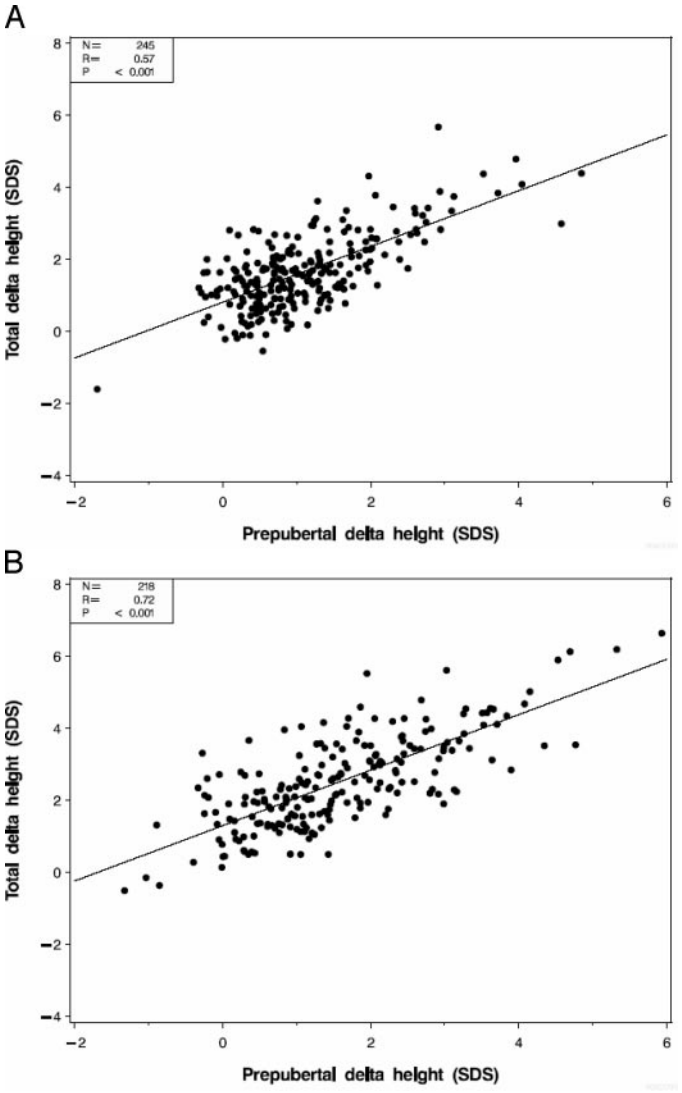

FIG. 5. Relationship between prepubertal change in height SDS and total change in height SDS between the start of GH treatment and near-FH in children with idiopathic GHD. A, Data in children with IGHD; B, data in children with MPHD.

tential. The GH dose in all European trials was approximately 0.18 mg/kg·wk, whereas the Genentech data from the United States was based on a GH dose of 0.3 mg/kg·wk. The general similarity of height outcomes, however, suggests that the GH dose has a finite impact, although earlier treatment with the higher dosing may lead to improved responses with greater catch-up growth. Total GH exposure during the prepubertal years may be a significant factor.

When examining data from large national or international registries, one should bear in mind the potential limitations of such databases. Although more representative of the general practices of a broad range of pediatric endocrinologists than strictly controlled research trials, inherent variability is present. The criterion for diagnosis of GHD (*i.e.* peak GH level <10 ng/ml on standard provocative testing) seems consistent, but factors such as differing GH assays, the interpretation of such assay data, the use of GH-dependent peptides as part of the diagnostic paradigm, and the availability of sophisticated imaging techniques may lead to differing clinical conclusions (18). Children and peripubertal adolescents who test positive for GHD may have conditions such as constitutional delay of growth and maturation or may be in the spectrum of conditions referred to as IGF deficiency rather than classical GHD. The responses to GH treatment are likely to be modified in those circumstances.

In the past 5 yr, sophisticated mathematical models (19, 20) have examined many of the laboratory and auxological variables that may influence an individual's response to GH therapy. Ranke *et al.* (19) described the factors that appear to have an important effect on the initial response to GH treatment as well as growth during the first 4 yr of therapy. The present data from our large cohort of children reaching near-adult height confirm the relevance of auxological variables as well as results from GH stimulation tests, presumably a reflection of the severity of GHD, to longer-term growth. Besides the midparental height, which defines the genetic

potential of a child's growth, the magnitude of the first-year growth response, presumably a measure of sensitivity to GH, had the strongest correlation with the overall growth increment. The importance of the first-year growth response in predicting subsequent growth was initially suggested in the KIGS growth modeling study (19). Both that and the present study emphasize the importance of individual variability in the sensitivity to the effects of GH on the overall growth response. Studies of GH-induced production of IGF-I and IGF-binding protein-3 in children with GHD similarly show considerable variability in responsiveness (19, 21), supporting the suggestion that such biochemical differences may in part explain the wide ranges of long-term growth responses in GH-treated children with GHD. Recognition of such variability and the use of growth models to predict a child's response to therapy along with measurement of GH-dependent peptides (22–24) should help to optimize the long-term growth response to GH treatment. Because the only active intervention that the treating physician might use is dose alteration, careful individualization of the GH dose is an important factor in managing the prepubertal pattern of growth in patients with GHD.

Because age at onset of treatment is inversely correlated with the growth response, and smaller lighter children require lower doses of GH (with associated economic benefits), it is important to assess growth data from children treated at an early age. In short-term studies of 134 patients (25–27) treated before 3 yr of age, marked early catch-up growth occurred. The mean height gain was approximately 3 SDS after 4 yr of GH therapy, allowing most of these children to reach the normal height range by midchildhood. In one study in which GH treatment was started before 1 yr of age, mean height reached −0.4 SDS after 8 yr of treatment (27), and near-adult height in 13 patients treated before 5 yr of age did not differ from the midparental height (−0.9 *vs.* −0.7 SDS) (5). The current analysis emphasizes the importance of initiating GH treatment at a young age and of providing therapy over a long period of time, as confirmed by the strong correlation between the prepubertal height increment and the total height gain.

Another recent evaluation of the KIGS database focused on the factors that modify total pubertal growth in patients with IGHD (28). Although pubertal growth accounts for 20–35 cm of the height gain, it is clear from that study that the most successful strategies for enhancing GH-induced growth must concentrate on growth during early childhood rather than attempt to modulate the pubertal growth process. The patients reported in this study have not been exposed to pubertal dosing regimens (29). An assessment of the KIGS database (30) showed no benefit to FH with the use of GnRH agonists as a pharmaceutical attempt to alter the tempo of pubertal progression and skeletal maturation. Variations in definitions of the time of onset of puberty and changes in the actual onset of puberty, especially in adolescent females, with attendant changes in the time of occurrence of the pubertal growth spurt are likely to modify these findings further. Nonetheless, the key message from these data and the previously noted studies is that early and aggressive diagnosis and treatment of GHD are the most likely ways to achieve successful height outcomes in the most economically prudent fashion.

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