EVALUATION OF FIRST YEAR RESPONSE TO TREATMENT IN CASES WITH GROWTH HORMONE DEFICIENCY

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Abstract

Background/Aims. Growth hormone (GH) treatment has severe cost burden on patients, their families, and healthcare systems. Therefore, accuracy of diagnosis should be confirmed; factors affecting the response to treatment should be defined. The present study is performed to evaluate auxiliary diagnostic parameters and factors affecting treatment in growth hormone deficiency (GHD).

Methods. In this study, 142 patients under the age of 16, with at least one year of treatment, were included. Treatment dose of somatropin was 0.2 mg/kg/week in all cases. Response to treatment was evaluated by measuring annual height and height standard deviation score (SDS) gains every 3 months.

Results. Male to female ratio was 79 to 63, and follow-up duration before the treatment was 0.89 ± 0.38 years. Annual growth rate before the treatment was 2.92 ± 1.02 cm, and age at the treatment initiation was 9.97 ± 3.22 years. Height gain SDS at the end of the first year was significantly higher in cases which were at the prepuberty, had severe short stature, low height SDS-mid parental height SDS (HSDS-MPHSDS), and initiated treatment at earlier ages. Correlations in height gain and height SDS gain at the end of the first year were significant between bone age at treatment baseline, delta SDS factors, L-dopa and clonidine stimulation results (both are $p < 0.01$).

Conclusion. Height gain was positively related to body mass index, whereas negatively to bone age at treatment baseline, responses obtained from stimulation tests, and delta SDS values. In the treatment evaluation, the parameters which can affect according to model chosen by the investigator, may differ.

Key words: body mass index, growth disorders, body height, human growth hormone, child.

cause is not defined in majority of the cases, and it is defined as idiopathic growth hormone deficiency (IGHD). Signs of congenitally related GHD, like micropenis/hypoglycemia, are detected in the first few months and/or years of life. Early diagnosis is important for prevention of late complications of hypoglycemia and catch-up growth (1). Growth is severely retarded in IGHD cases diagnosed at older ages. Acquired causes include trauma, central nervous system malformations, and intracranial masses. Whatever the underlying reasons of cases with growth hormone deficiency are, growth hormone stimulation test is recommended to be performed after exclusion of chronic systemic diseases along with bone age examination, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein (IGFBP), and thyroid function tests (2). Although cut-off values of stimulation tests are variable according to the sites, values below 10 ng/mL are accepted to indicate unresponsiveness (3). Although the treatment varies according to underlying causes, use of recombinant GH of 25-100 µg/kg/day doses are recommended (4).

Growth hormone treatment has severe cost burden on patients, their families, and healthcare systems. Therefore, accuracy of diagnosis should be confirmed; factors affecting the response to treatment should be defined; treatment of unresponsive cases should be re-evaluated; and inappropriate treatment costs should be avoided. The present study is performed to evaluate auxiliary diagnostic parameters and factors affecting the treatment in GHD cases.

PATIENTS AND METHODS

In this study, 142 patients data under the age of 16 with at least one year of treatment were evaluated retrospectively. The study was approved by the local ethics committee of Gaziantep University. Patients who

INTRODUCTION

Although growth hormone deficiency is related to many causes either congenital or acquired, still the

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received chemotherapy/radiotherapy for any reasons, biologically inactive GH, neurosecretory dysfunction, growth hormone resistance, growth hormone deficiency due to acquired causes, chronic systemic disease, and syndrome stigmata, were excluded. Height; height standard deviation score (SDS); weight; weight SDS; Body mass index (BMI); familial targeted height; familial targeted height SDS; height SDS-mid parental height SDS (HSDS-MPHSDS); height, height SDS and height SDS gains were calculated at the end of the 3th, 6th month, 1st year of treatment in all of the cases. Serum IGF-1 concentrations were assessed by Immulite, DPC assays; WHO NIBSC 1st IRR 87/518 standard was applied, with analytical sensitivity 20 ng/mL, calibration range up to 1600 ng/mL, intra-assay coefficient of variation (CV) -3.1-4.3% and inter-assay CV -5.8-8.4%. Serum IGFBP3 were determined using a two-site chemiluminescent enzyme immunometric assay, CV of inter and intra-assay 4.2-8.3 and 5.3-6.7% respectively. The concentrations of GH were measured by the two-site chemiluminescent enzyme immunometric assay, calibrated two WHO IRP 80/505 standard. The intra-assay CV of 5.3-6.5% and the inter-assay CV of 5.5-6.2%. Growth hormone stimulation tests were performed in all of the patients by using clonidine and L-DOPA. Clonidine 75 µg/m² (maximum of 150 µg) and L-DOPA 10mg/kg (maximum of 500mg) orally were administered. Blood sample was obtained at 0, 30, 60, 90 minutes. If the response level was below 3 ng/mL, it was defined as severe GHD; if it was between 3-7 ng/mL, it was defined as intermediate GHD; and if it was between 7-10 ng/mL, it was defined as mild GHD. Central hypothyroidism and corticotroph axis was evaluated on local laboratory references. Hypothyroidism was defined as low or low-normal serum TSH concentration and low serum-free T4 and free T3 concentrations. ACTH deficiency was defined as a morning serum cortisol concentration of less than 5 µg/dL. Hypogonadism was confirmed in both

sexes by lack of puberty and no increase in FSH and LH in response to GnRH. Hypophyseal magnetic resonance imaging (MRI) was performed in all of the cases with GHD diagnosis. During treatment, four drugs, which were available in Turkey, and had the active substance of somatropin, were used. Informed consent was obtained from all patients or their parents. Treatment doses were 0.2 mg/kg/week in all cases. Response to treatment was evaluated by measuring annual height and height SDS gains every 3 months.

Data were analyzed by using Statistical Package for Social Sciences (SPSS), version 13.0. Frequency distribution was used to define the sample, and mean±standard deviation was used for continuous data. Means of groups were compared by using Student's-t test. One way analysis (ANOVA) was employed to compare multiple group means, and Tukey test (among post hoc tests) was employed in dual comparisons of the groups, which were significant as the result of variant analysis ($p<0.05$). Linear regression test was employed to evaluate collective effects of multiple independent variables on dependent variables. The accepted level of significance was at $P<0.05$.

RESULTS

During this study, 142 patients had at least one year of rHGH treatment. Male/female ratio was 79/63, and follow-up duration before the treatment was 0.89 ± 0.38 years. Annual growth rate before the treatment was 2.92 ± 1.02 cm, and age at the treatment initiation was 9.97 ± 3.22 years. All cases were investigated by the pituitary MRI for anatomical defects and pathological findings were detected in 35 (24.6%) cases. Pituitary hypoplasia in 22 (15.5%), partial empty sella syndrome in 11 (7.7%) and ectopic posterior pituitary in two (1.4%) children were found. General characteristics of cases are shown in Table 1.

Table 1. General characteristics of cases

Mean age (years)	9.97±3.22	Age at treatment initiation	<6 yrs	22 (15.5%)
Gender	F/M:63/79		6-11 yrs	59 (41.5%)
Pretreatment follow-up duration (years)	0.89±0.38		>11 yrs	61 (43%)
Pretreatment GV (cm/years)	2.92±1.02	Hypothoidism	Present	17 (12%)
MPH (cm)	164.40±7.95		Absent	125 (88%)
MPH SDS	-0.96±0.72	Pubertal signs	Present	44 (31%)
Height (cm)	117.29±17.61		Absent	98 (69%)
HSDS	-3.46±1.18	Severe short stature	Present	57 (40.1%)
Height Age (years)	6.5±2.77		Absent	85 (59.9%)
Bone Age (years)	6.69±3.13		Normal	107 (75.4%)
Weight (kg)	24.58±10.59	Hypophyseal MRI	Pituitary hypoplasia	22 (15.5%)
BMI (kg/m ²)	17.05±3.43		Partial empty sella syndrome	11 (7.7%)
HSDS-MPHSDS	-2.49±1.39		Ectopic posterior pituitary	2 (1.4%)

Patient responses to laboratory and growth hormone stimulation tests were as follows: 81.7% responded IGF-1 at -2 SDS; 91.5% responded IGFBP-3 below -2 SDS; 79.6% responded the stimulation test with L-dopa <3 ng/mL, and 64.1% responded the stimulation test with clonidine <3 ng/mL (Table 2).

Growth velocity (GV) in the first 6 months of treatment was 11.42 ± 2.89 cm/yr. HSD gains at the end of first years were 0.80 ± 0.45 (Table 3).

While height gain at the end of the first year of treatment was not changed in respect to gender, pubertal status, degree of short stature and HSDS-MPHSDS, it was higher in cases which had hypothyroidism and initiated treatment earlier. While height gain SDS at the end of the first year was not statistically significantly different in cases with respect to gender, presence of hypothyroidism, IGF1 SDS and response to GHST, it was significantly higher in cases which were at the prepuberty, had severe short stature, low HSDS-MPHSDS and initiated treatment at earlier ages (Table 4).

While there was no difference in maturity degree of bone age, IGF-1 SDS, responses against clonidine and L-dopa stimulation tests between the height and height SDS gains, both height and height SDS gains were detected higher in cases with low IGFBP-3 levels (Table 4).

The 37% of height gain at the end of the first

year was provided according to BMI, bone age at the treatment baseline, L-dopa, clonidine values and delta SDS factors. The correlation between the variables was statistically significant at the level of $p < 0.01$. The 29% of height SDS gain at the end of the first year was provided according to BMI, bone age at the treatment baseline, L-dopa, clonidine values and delta SDS factors. The correlation between the variables was statistically significant at the level of $p < 0.01$ except for the BMI, which did not contribute significantly in the height SDS gain at the end of the first year (Table 5).

DISCUSSION

Considering its psychological and physical effects on individuals, early diagnosis and treatment of short stature owing to growth hormone deficiency are crucially important because it is a treatable disease. Ranke *et al.* (5) reported that the age at the initiation of treatment for cases with and without severe GHD was 6.44 and 6.86 years, respectively, whereas Reiter *et al.* (6) reported it to be 9.3-11.7 years. In our study, the age at the initiation of treatment was noted to be 9.97 ± 3.22 years, and the factors affecting treatment and initiation of treatment were awareness of parents, socioeconomic status of the family, and accessibility of healthcare services. In previous studies, the pretreatment HSDS value has been reported to be -2.65-3.1 (8-9), whereas

Table 2. Laboratory characteristics of cases

		mean/n	%
IGF-I (ng/mL) (mean $\pm$ SD)		76.24 $\pm$ 61.0	
IGF-I SDS group	-1,-2	26	18.3
	<-2	116	81.7
IGFBP-3 (mg/L) (mean $\pm$ SD)		2.56 $\pm$ 0.91	
IGFBP-3 SDS group	-1,-2	12	8.5
	<-2	130	91.5
L-dopa (mean $\pm$ SD)Response (ng/mL)		3.95 $\pm$ 1.76	
	<3	113	79.6
Maximum response to L-dopa(ng/mL)	3-7	23	16.2
	7-10	6	4.2
Clonidine (mean $\pm$ SD) Response (ng/mL)		4.53 $\pm$ 2.07	
	<3	91	64.1
Maximum response to Clonidine (ng/mL)	3-7	32	22.5
	7-10	19	13.4

Table 3. Height and height SDS gains according to treatment duration

	n	Mean $\pm$ SS
Pretreatment annual growth velocity (cm)	142	2.92 $\pm$ 1.02
Annual growth velocity in 0-6 months (cm)	142	11.42 $\pm$ 2.89
Annual growth velocity in 6-12 months (cm)	142	8.55 $\pm$ 2.48
Height gain at the end of 1 st year (cm)	142	9.92 $\pm$ 2.44
SDS gain at the end of 1 st year	142	0.80 $\pm$ 0.45

Table 4. Treatment responses of cases according to their clinical situations

		Height gain at the end of 1st year	<i>P</i>	Height SDS gain at the end of 1st year	<i>P</i>
Gender	F (63)	9.76±2.51	0.314	0.75±0.39	0.242
	M (79)	10.04±2.38		0.84±0.50	
Hypothyroidism	Present (17)	11.15±2.64	0.031	0.89±0.60	0.406
	Absent (125)	9.83±2.31		0.79±0.43	
Puberty	Present (44)	9.78±2.19	0.485	0.86±0.43	0.031
	Absent (98)	10.08±2.46		0.68±0.49	
Severe short stature	Present (57)	10.06±2.46	0.747	0.67±0.42	0.004
	Absent (85)	9.93±2.34		0.89±0.46	
	≥-1.5 (28)	9.86±2.36		0.69±0.46	
HSDS-MPHSDS	-1.5,-2.5 (44)	9.38±2.41	0.071	0.66±0.40	0.002
	<-2.5 (70)	10.42±2.31		0.94±0.45	
	<6 yrs (22)	12.17±2.62		1.10±0.46	
Age	6-11 yrs (59)	9.35±1.91	<0.001	0.80±0.42	0.002
	>11 yrs (61)	9.82±2.27		0.70±0.45	
	2-3yrs (75)	10.20±2.53		0.44±0.05	
CA-BA	3-4 yrs (43)	9.62±2.06	0.096	0.47±0.07	0.098
	4-5 yrs (14)	9.07±2.16		0.44±0.12	
	>5 yrs (10)	11.20±2.27		0.42±0.13	
Hypophyseal MRI	Pathological (35)	10.63±2.99	0.063	0.92±0.58	0.086
	Normal (107)	9.77±2.12		0.77±0.40	
IGF-I SDS	-1,-2 (26)	10.77±2.76	0.063	0.83±0.37	0.732
	<-2 (116)	9.81±2.26		0.80±0.47	
IGFBP-3 SDS	-1,-2 (12)	8.39±2.12	0.015	0.54±0.42	0.034
	<-2 (130)	10.13±2.35		0.83±0.45	
	<3 (113)	10.09±2.43		0.85±0.46	
L-Dopa response	3-7 (23)	9.52±1.95	0.807	0.37±0.78	0.315
	7-10 (6)	9.78±3.1		0.53±0.21	
Clonidine response	<3 (91)	10.18±2.36	0.465	0.88±0.48	0.061
	3-7(32)	9.47±2.35		0.62±0.39	
	7-10 (19)	9.95±2.52		0.75±0.32	

Table 5. Factors affecting height and height SDS gains at the end of the first year

	Height gain at the end of 1st year		Height SDS gain at the end of 1st year	
	B	<i>p</i>	B	<i>p</i>
BMI	0.148	0.009	0.008	0.498
Bone age at treatment initiation	-0.152	0.015	-0.039	0.002
L-dopa response	-0.427	<0.001	-0.047	0.033
Clonidine response	-0.237	0.009	-0.041	0.024
HSDS-MPHSDS	-0.260	0.041	-0.069	0.007

in the present study, it was observed to be -3.46 ± 1.18 . The reason for this difference might be the age at the initiation of treatment, GHD severity and duration, as well as ethnic background.

In a study by Kalina *et al.* (10), hypophyseal anatomic disorder detected using MRI examinations was reported in 25.9% of the cases treated for GHD, whereas it was reported in 53% of IGHD cases and 79% of MPHD cases in another study (11). In the present study, all cases were investigated by the pituitary MRI for anatomical defects and pathological findings were detected in 35 (24.6%) cases. Because the anatomical disorder rate has been quite high, MRI examination should be performed in cases diagnosed with GHD.

A research conducted in Thailand (12) indicated IGF-1 SDS and IGFBP-3 SDS to be -0.6 ± 0.8 and -1.6 ± 1.3 at baseline, respectively. In addition, the changes in IGF-1 and IGFBP-3 levels were also evaluated. At the end of the first year of treatment, eight of the nine children with IGF-1 SDS ≥ 1 exhibited good response, whereas six of the 10 children with IGF-1 SDS < 1 exhibited poor response, indicating that the change in IGF-1 SDS at the first year of treatment (≥ 1) could predict the response with a sensitivity of 88.9% and specificity of 60%. In the present study, we did not evaluate the gain in height or HSDS owing to changes in the IGF-1 levels. In a previous study, Cohen *et al.* (13) reported that IGF-1 SDS was -3.56 ± 1.74 in all

patients and -3.75 ± 2.08 in the low group, -3.57 ± 1.47 in the high group, and -3.17 ± 1.44 in the conventional group and demonstrated that the change in HSDS from baseline is positively correlated with both the IGF-1 SDS change from baseline and cumulative GH dose. In another study that investigated the effects of dose and gender on the growth and growth factor response of GHD children, IGFBP-3 SDS was reported to be -1.8 ± 1.5 in all groups at baseline. Furthermore, IGF-1 and IGFBP-3 SDS were found to be significantly correlated with the gain in HSDS while on therapy (14). In the present study, IGF-1 and IGF-1 SDS were 76.24 ± 61.0 ng/mL and <-2 in 116 cases (81.7%), respectively, whereas IGFBP-3 and IGFBP-3 SDS were 2.56 ± 0.91 mg/L and <-2 in 130 cases (91.5%), respectively. These values are considered to be low, similar to those demonstrated in previous studies. Moreover, no relationship was found between the IGF-1 level and gain in height and HSDS at the end of the first year of treatment. However, the gain in height and HSDS was significantly higher in the low IGFBP-3 (SDS <-2) group (10.13 ± 2.35 cm and 0.83 ± 0.45 , respectively) when compared with that noted in mildly low IGFBP-3 (SDS between -1 and -2) group at baseline (8.39 ± 2.12 cm and 0.54 ± 0.42 , respectively).

Growth hormone stimulation tests can be performed using ITT, arginine, clonidine, pyridostigmine, and L-dopa. Although the diagnostic cutoff values for these tests vary in different studies (9,14-15) (e.g., 3.3, 4.5 ± 2.9 , 4.9 ± 2.7 , and 5.6 ± 2.7 ng/mL), GHD diagnosis can be confirmed if two test results are <10 ng/mL. In the present study, the mean response rates to L-dopa and clonidine were 3.95 ± 1.76 and 4.53 ± 2.07 ng/mL, respectively, similar to those obtained in previous studies. However, we did not find any statistically significant differences between the response to GHSTs and gain in height or HSDS.

In earlier studies, pretreatment growth velocity (PGV) has been reported to be 3.9-4.0, 4.8 ± 2.4 , and 3.6-5.2 cm/year (14,16-18) and the height gain at the end of the first year of treatment has been observed to be 9.3, 8.1-9.3, 8.21 ± 1.62 , and 9.2 cm (12,19-21). In the present study, an rhGH dose of 0.2 mg/kg/week was employed and the annual PGV was 2.92 ± 1.02 cm/year. Furthermore, the annual growth rate was 11.42 ± 2.89 cm/year in the first 6 months of treatment, whereas it was 8.55 ± 2.48 cm/year in the second 6 months of treatment. The mean height and SDS gains in the first year of treatment were 9.92 ± 2.44 cm/year and 0.80 ± 0.45 , respectively. The differences in the height gain reported in various studies may be owing

to factors, such as age at the initiation of treatment, heterogeneous study groups, rhGH dose applied, and genetic characteristics of the subjects. Krström *et al.* (22) showed that the HSDS gain at the end of the first year of treatment was 0.72 (0.3-2.26); Ranke *et al.* (23) reported it to be 1.04 ± 0.68 and 0.72 ± 0.42 in cases with severe and mild-to-moderate GHD, respectively; and Lee *et al.* (24) indicated it to be 0.61 ± 0.49 in cases with IGHD. In the present study, the HSDS gain was found to be 0.80 ± 0.45 at the end of the first year of treatment. Thus, HSDS gain may differ owing to factors, such as age at the initiation of treatment, the rhGH dose applied, severity of GHD, and pubertal development stage.

An earlier study reported that the HSDS gain at the end of the first year of treatment in cases with multiple hypophyseal deficiencies (MHDs) was 0.85 ± 0.76 (25). Furthermore, evaluation of the treatment responses of IGHD and MHD cases using data from KIGS database at the end of the first year of treatment revealed that HSDS gains in IGHD and MHD cases were 0.7 (0.3-1.3) and 0.9 (0.4-1.9), respectively, with the values exhibiting statistically significant difference ($p < 0.001$) (25). In the present study, the height gain at the end of the first year of treatment in MHD cases with hypothyroidism and GHD was 11.15 ± 2.64 cm, whereas that in MHD cases without hypothyroidism was 9.83 ± 2.31 cm ($p = 0.031$). Moreover, the HSDS gain was 0.89 ± 0.60 ($p = 0.406$). It must be noted that the greater height gain in cases with hypothyroidism, when compared with that in cases with isolated GHD, may be related to the interaction between L-thyroxine and GH as well as owing to L-thyroxine effects.

Bang *et al.* (26) indicated that the height gain at the end of the first year of treatment in prepubertal cases with IGHD was 9.1 (7.8-10.2) cm/year, whereas that in the total study group was 8.7 (7.5-9.9) cm/year, with the values presenting no statistically significant difference. Furthermore, the HSDS gains at the end of the first year of treatment were 0.74 (0.46-0.97) in the IGHD group and 0.65 (0.40-0.90) in the total study group. In the present study, the height gain at the end of the first year of treatment was 10.08 ± 2.46 and 9.78 ± 2.19 cm/year in prepubertal and pubertal cases, respectively ($p = 0.485$), whereas the HSDS gain was higher in the pubertal group (0.86 ± 0.43) when compared with that in the prepubertal group (0.68 ± 0.49) ($p = 0.031$).

In an earlier study in which there were no differences in the age of subjects at treatment initiation, GH dose applied, bone age retardation degree, BMI,

HSDS, and basal IGFBP-3 levels, 202 A/C IGFBP-3 mutations and treatment responses were evaluated. The results revealed that the increase in the IGFBP-3 level was higher in the AA homozygote group during the treatment ($p = 0.002$), with greater height gain at the end of the first year of treatment, when compared with that in the heterozygote group (13.1 ± 2.1 cm, 11.4 ± 2.5 cm, and 10.8 ± 1.9 m, $p = 0.016$); however, no statistically significant difference was noted in adult height and HSDS between the groups (27). In the present study, genetic analysis was not performed; nevertheless, at the end of the first year of treatment, the height gain (10.13 ± 2.35 cm) and HSDS gain (0.83 ± 0.45) were found to be statistically significantly higher between cases with and without low IGFBP-3 levels ($p = 0.015$ and 0.034 , respectively) (Table 4). Further clarification of the molecular structures of the hormones and receptors affecting growth and adjustment of the treatment doses accordingly could provide more satisfactory responses. Ranke *et al.* (5) classified GHST responses as <5 and $5-10$ ng/mL and found that the height gain (10.39 ± 3.08 and 8.58 ± 2.07 cm, respectively) and HSDS gain (1.11 ± 0.69 and 0.74 ± 0.43 , respectively) at the end of the first year of treatment were higher in the group with lower GH response but without any statistically significant difference (5). In the present study, the responses to GHSTs were classified as <3 , $3-7$, and $7-10$ ng/mL and similar to the findings of Ranke *et al.* (5), the height and HSDS gains at the end of the first year of treatment year were higher but without any statistically significant difference in the group with low GH response (Table 4).

On evaluating the effects of different treatment doses on height gain, it has been demonstrated that age at the initiation of treatment and treatment dose were the most influencing factors at the end of the first year of treatment (28). Furthermore, Ranke *et al.* (29) reported that height gain at the end of the first year of treatment was related to GH dose, age, weight SDS, and HSDS-MPHSDS. In the present study, 37% of height gain at the end of the first year of treatment was positively related to BMI but negatively related to bone age at the treatment baseline, responses to GHSTs, and delta SDS values.

In conclusion, nevertheless, it must be noted that in treatment evaluation, the parameters which can affect according to the model chosen by the investigator, may differ.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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