Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

The predictors of growth response to growth hormone therapy in growth hormone deficient Egyptian children

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ARTICLE HISTORY

Received: 16.09.2015

Accepted: 13.10.2015

Available online: 30.12.2015

Keywords:

bone age, growth hormone deficient, growth hormone therapy, predictors

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ABSTRACT

Short stature is one of the most common concerns presenting to pediatric endocrinologists and other physicians caring for children. Our aim is to identify the predictors of growth response to Growth hormone in GHD children. Factors (demographic, auxological) that may determine the response to GH therapy in 449 (GHD) patients followed for 4 years. Males and females with a mean age at the start of therapy of 11.9±3.4 years and 11.4±2.7 years for males and females respectively. Only 98 patients were followed for 4 years and the delta changes of them showed; height was significantly improved from 4.1 to 2.9 (p-value = 0.0001) and their GV were significantly decreased from 9 cm (5.2 SDS) to 5.4 cm (1.1 SDS) (p-value = 0.0001) of catch up growth during the first two years of GH therapy, height and weight deficit, GH peak levels and bone age delay were the main predictors.

INTRODUCTION

Many factors affect the growth response to recombinant human growth hormone (rhGH)some of which are unknown [1-2]. The predicted adult height may be inaccurate in individuals but can be helpful together with other criteria (family pubertal history and midparental target height) in deciding to treat with GH. [3]A variety of models have been proposed to predict long-term response to rhGH therapy [4-9].

We are aiming to evaluate different factors (demographic and auxological) that may affect the response to GH therapy in GHD patients to determine the predictors of growth response to rhGH to reach an optima response to therapy.

MATERIALS AND METHODS

PATIENTS

Four hundred and forty nine patients with short stature, receiving GH therapy, were included in this study; 317 males (70.6%) and 132 females (29.4%). Their mean age was 11.9±3.4 years in males and 11.4±2.8 years in females. They were selected over four years period. The study was done at Diabetes Endocrine Metabolism Pediatric Unit (DEMPU), Children Hospital Cairo University.

All patients had the inclusion criteria of a stature more than 2 SD below the mean and, if available, a growth velocity (monitored over 6-12 months) below the tenth centile for age and sex. .The peak growth hormone level below 10 ng /ml by Clonidine and insulin tolerance tests, isolated or associated with other pituitary hormone deficiency. Exclusion criteria were Patients with short stature due to idiopathic short stature, Turner syndrome, chronic systemic disease, malnutrition, bonedysplasias or prenatal causes.

Methods

Informed consent was taken from the parents of childrenaccordingto guideline of ethical committee of National Research Centre, Egypt. All cases were subjected to full history taking and clinical examinations. A detailed family history was undertaken for consanguineous marriage or similar cases in first or second degree relatives.

Full anthropometric evaluation was also done, including target and mid-parental heights. Target height was calculated by the method of Tanner *et al.*, taking the average of mother's and father's height after adding of 13 cm in boys or subtractions of them in girls, while mid-parental height is calculated as before ± 6.5 cm. [10].All anthropometric measurements and calculation, bone age and radiological evaluation were done as mentioned before in Ismail et.al. [11-12]

Laboratory investigations included

1. Hypothyroidism was excluded by evaluating thyroid profile (FT3, FT4, and TSH).

2. *Routinelaboratorytests*which include complete blood picture, renal and liver function tests.

3. Provocation tests (clonidine and insulin tolerance test) separated by one-week interval and analysis by Immunoradiometric assay (IRMA) were done to evaluate GH [11-12].

Treatment protocol

All patients received biosynthetic growth hormone therapy with a standard dose of 20 IU /m2/week divided on 6days [11].

FOLLOW UP:

The same system mentioned in Ismail et.al, for follow up andCompliance to therapy [11].

STATISTICAL ANALYSIS:

The statistical package for SPSS software computer program version12 was used for data analysis. Quantitative data were presented as mean ± SD, range, frequencies and qualitative data as percentage. For comparison of two groups, the Student's t-test for dependent and independent variables was used. Significant P-value was considered if it is less than or equal to 0.05.

For predictors of growth response, linear regression analyses were performed. (height velocity cm/year after 12 months of GH therapy was treated as dependent variable and demographic, auxological parameters as independent variables). For each parameter, the result of the two-point yielding maximum r^2 is included.

RESULTS

Demographic data:

Four hundred and forty nine short children (GHD) were referred to (DEMPU), for GH therapy, with a mean age at onset of 8.3±3.4 years .CA at onset of therapy 11.8±3.2 years, BA at onset of therapy 9.2±3.4 years and BA delay of 2.5±1.6 years. They were sub-classified according to the etiology into four subgroups: Idiopathic GHD**:** Patients of this group showed no etiological cause. They represent the majority of cases (360 cases or 80.2 %). Their mean age was 11.7±3.3 years. Organic GHD: Their CT finding revealed an acquired space occupying lesions such as brain tumor, cyst or hydrocephalus. They were 25 cases (5.6 %), their mean age was 13.3±3.1 years.Familial GHD: They were described as familial GHD if their mother or father's height is less than three SDS below the mean for age and sex or if there are similar cases among first or second degree relatives. They were 54 cases (12 %), their mean age was 11.6±3.0 years.Developmental GHD: These patients showed either atrophic sella or a hypoplastic pituitary gland diagnosed by cranial CT scan. They were 10 cases (2.2 %), their mean age was 11.7±2.9 years.

In (GHD), 374 (83.3%) patients have isolated GHD, whereas 75 (16.7%) patients have multiple pituitary hormone deficiency. In (GHD), 374 (83.3%) patients have isolated GHD, whereas 75 (16.7%) patients have multiple pituitary hormones.

Descriptive statistic was presented in table (1) for patients with GHD.

Table (2) illustrates basal auxological and skeletal maturity data of patients with complete a The patient's height became much closer to the target height as the difference changed from 43.7 to 19.6 cm (3.1 to 1.7 SDS) in GHD and partial GHD. Estimated mature height was improved from 152.7 to 162.5 cm in GHD.The growth velocity was decreased from 9 cm (5.2 SDS) in the first year to 5.4 cm (1.1 SDS) in the fourth year of follow up for GHD.

Comparative studies:

Patients with GHD followed for 4 years (98 patients) were compared, using ANOVA showed a significant difference for height SDS; target height patient's height (cm & SDS), growth velocity SDS, height gain and estimated mature height (P- value = 0.0001 for all).

Patients with complete GHD (286 patients) were compared to

Table 1: FAnthropometric, Skeletal Maturity and Laboratory Data of All Patients with Growth Hormone Deficiency

Variables	Basal	First year	Second year	Third year	Fourth year
	Mean ± SD n = 449	Mean ± SD n = 448	Mean ± SD n = 305	Mean ± SD n = 160	Mean ± SD n = 98
Height (SDS)	- 4.1 ± 1.5	- 3.4 ± 1.3	- 3.1 ± 1.4	-2.9 ± 1.5	-2.9 ± 1.6
Growth velocity (cm)		9.0 ± 2.6	7.2 ± 2.2	5.8 ± 2.2	5.4 ± 1.7
Growth velocity (SDS)		5.2 ± 4.8	3.8 ± 5.2	2.4 ± 4.8	1.1 ± 3.3
Target height – height (cm)	43.7 ± 18.1	34.4 ± 17.2	27.4 ± 16.1	23.3 ± 13.8	19.6 ± 12.6
Target height – height (SDS)	3.1 ± 1.5	2.3 ± 1.4	2.0 ± 1.4	1.8 ± 1.4	1.7 ± 1.4
Height gain (SDS)		0.7 ± 0.5*	0.4 ± 0.5**	0.3 ± 0.4***	0.2 ± 0.4****
EMH (cm)	152.7 ± 10.6	156.8 ± 9.7	159.3 ± 10.1	161.0 ± 10.2	162.5 ± 10.7
Delta BA/CA		0.8 ± 0.2	0.9 ± 0.3	1.0 ± 0.2	1.1± 0.2

Height gain (SDS) = Height 1st year SDS Height basal SDS
BA: bone age CA: Chronological age
EMH: Estimated mature height.* P-value is significant < 0.05

Table 2: Auxological and Skeletal Maturity Data in Patients With Complete and Partial Growth Hormone Deficiency at Onset of Therapy

Variables	Complete GHD	Partial GHD	P-value
	Mean ± SD n = 286	Mean ± SD n = 163	
Height (SDS)	-4.5 ± 1.5	- 3.5 ± 1.1	0.0001*
Weight (SDS)	- 3.1 ± 1.8	- 2.6 ± 1.5	0.003*
Weight/height (SDS)	0.6 ± 2.1	0.1 ± 2.1	0.02*
US/LS (SDS)	0.6 ± 1.6	0.2 ± 1.4	0.002*
Triceps (SDS)	0.1 ± 1.4	- 0.4 ± 1.0	0.0001*
Subscapular (SDS)	0.6 ± 1.5	- 0.05 ± 1.1	0.0001*
Target height (SDS)	- 1.1 ± 0.8	- 1.2 ± 0.8	0.001*
Target height SDS – height basal SDS	3.5 ± 1.5	2.3 ± 1.3	0.0001*
Growth velocity (SDS) 1st year	6.0 ± 5.0	3.7±4	0.0001*
Height gain (SDS)	0.8 ± 0.6	0.5 ± 0.4	0.0001*
BA Delay (year)	2.8 ± 1.6	2.1 ± 1.4	0.0001*
Delta BA / CA	1.1 ± 4.9	0.8 ± 0.2	0.5
EMH basal (cm)	151.1 ± 11.4	155.5 ± 8.4	0.0001*
EMH 1st year (cm)	156.1 ± 10.5	158.1± 8.1	0.02*
EMH 2nd year (cm)	159.2 ± 10.5	159.5 ± 9.3	0.8
EMH 3rd year (cm)	160.7 ± 10.7	161.7 ± 9.0	0.6
EMH 4th year (cm)	162.7 ± 11.1	161.8 ± 10.1	0.7

US/LS: Upper segment/ lower segment
BA: bone age CA: Chronological age
P-value is significant if < 0.05

Height gain = Height 1st year SDS Height basal SDS
EMH: Estimated mature height.

Table 3a: Prediction of Growth Response in (First and Second year)

Variables	first year			second year		
	parameter estimar	Ranke	% variability	parameter estimar	Ranke	% variability
Interapt (constant)	-0.74			-8.21		
Target height(SDS) - height(SDS)						
Height(SDS)	0.06	1	16	-0.63	4	9
weight(SDS)	-1.24	2	9	0.86	3	9
CA (year)	0.24	3	9			
BA (year)				0.78	2	16
BA delay (year)	0.28	4	4			
Insulin maximum GH(Ug/L)	-0.37	6	4			
1st year GV (cm/year)				0.7	1	49
2nd year GV (cm/year)						
3rd year GV (cm/year)						
r^2	0.27			0.68		
Error SD(cm)	4.4			3.5		

Table 3b: Prediction of Growth Response in GHD (Third and Fourth year)

Variables	third year			fourth year		
	parameter estimar	Ranke	% variability	parameter estimar	Ranke	% variability
Interapt (constant)	0.58			2.08		
Target height(SDS) - height(SDS)				-0.84	2	25
Height(SDS)	2.1	5	9			
weight(SDS)	-2.48	6	4			
CA (year)	-0.12	2	25			
BA (year)						
BA delay (year)				-0.02	3	9
Insulin maximum GH(Ug/L)						
1st year GV (cm/year)	-0.53	3	9			
2nd year GV (cm/year)	1.38	1	49			
3rd year GV (cm/year)				0.42	1	49
r^2	0.9			1		
Error SD(cm)	4					

Table 4: Data of Patients with GHD Who Reached Final Adult Height

Variable	Male			Female		
	Mean±SD	Minimum	Maximum	Mean±SD	Minimum	Maximum
Final Adult Height (cm)	162±6.4	154.2	169.3	148.3±6.1	140.8	162.2
Final Adult Height (SDS)	(-1.9=1.1)	-3.1	-0.8	(-2.3±1)	-3.6	0
FAH-EMH (cm)	10.4±6.7	19.3	3.2	9.0±7.0	21	1.4
Target height-FAH (cm)	5.9=6.4	-3	11.3	6.8±5.7	-2.2	16.5
Target height(SDS)-FAH (SDS)	0.9=1.1	-0.5	1.7	1.1±0.9	-0.3	2.8
Near Final Adult Height (cm)	159.8±7.4	151.4	169	146.4±5.7	139.6	158
Near Final Adult Height (SDS)	(-2.2=1.1)	-3.5	-0.9	(-2.6±0.9)	-3.8	-0.7
FAH-Near FAH (cm)	2.2=1.3	0.3	3.2	1.97±1.1	0.8	4.2

patients with partial GHD (163 patients) for auxological parameters at onset of therapy (table 2). It showed a significant difference for height SDS (P- value = 0.0001), growth velocity (P- value = 0.0001), height gain (P- value = 0.0001), bone age delay (P- value = 0.0001), EMH at onset and after the 1st year (P- value = 0.0001 and 0.02).

The delta changes for patients with complete GHD who were followed for 4 years, showed a significant difference in height SDS, target height- height (cm), target height- height (SDS), GV, height gain and EMH (P- value = 0.0001 for all parameters . Also, patients with partial GHD showed a significant difference for the same parameters with P value of 0.007, 0.0001, 0.006, 0.04, 0.0001 and 0.04, respectively.

Prediction models:

For the prediction of growth response in GHD during the 4 years of treatment a regression equation was summarized in table (3a, b) where the r^2 was 0.27, 0.68, 0.9 and 1 in GHD with SD error (cm) of 4.4, 3.5 and 4 for the 1st, 2nd, 3rd and 4th years, respectively.

Final or near final adult height**:** table (4).

DISCUSSION

Bone age was delayed by 2 SD or more (i.e. 2 years or more) in patients with GHD. Similarly, other studies[4, 13, and 14]reported a BA delay of more than 2 years in cases with GHD. Ranke et al (1999) reported growth response after 4 years of GH therapy similar to ours, with a growth velocity of 9.2±2.3,7.3±1.5,6.5±1.3 and 6.2±1.1 cm/year during 1st, 2nd, 3rd and 4th years, respectively[4]. Merico et al (2000) reported 11.2±0.7 and 6.0±1.2cm during 1st and 2nd years of GH treatment [15].During the period of 4 years study, spontaneous puberty within our group of GHD patients was reported at age 11.9±1.9 years for girls and age 12.4±1.9 years for boys during GH therapy. This is to be compared with the international figure reported in KIGS database [16] of 12.1 and 12.9 years in girls and boys, respectively. In the latter study, the mean age of induced puberty was 14.4 and 15.1 years, respectively, 10% of patients with idiopathic GHD had their puberty induced by sex steroid replacement.

The predictive factors were derived by the all possible regression approaches. Preliminary, this was applied for all cases of GHD, prepubertal and pubertal collectively. For the first year of GH therapy, height SDS, weight SDS, CA and BA delay at onset, IGF-1 and maximum GH values were the strongest predictors. Growth velocity was correlated positively to CA and BA delay at onset, and negatively correlated to height, weight SDS, IGF-1 SDS and maximum GH value; the higher the CA and BA delay at onset the better the growth velocity and the maximum GH values, the higher the growth velocity. For the first year, predictors explained 27% of the variability of the response with an error SD of 4.4 cm.

For the second year, first year growth velocity was the strongest followed by the BA. Height and weight SDS at onset were other predictors for the second year growth response. The higher the first year GV and the BA and the lower height and weight SDS at onset, the better is the growth velocity. For the 2nd year, predictors explained 68% of the variability of the response with an error SD of 3.5 cm.

For the third year, the strongest predictors were GV of 1st and 2nd years (2nd year response being stronger than 1st year response). CA, height and weight SDSwere other predictors. The higher the GV of 1st and 2nd years and the CA and the lower the height and weight SDS at onset, the better was the growth velocity. For the third year, predictors explained 90% of the variability of the response with an error SD of 4 cm.

For the 4th year, the strongest predictor factor was the 3rd year GV. The difference between target height SDS and the patient's height SDS, BA delay and IGFBP3 SDS were other predictors. The higher the 3rd year GV, the more the deviation from genetic height and the higher the BA delay , the higher is the growth response for the 4th year, predictors explained all the variability of the response.

It was evident that these patients were better analyzed. In the 1st year of GH therapy, height SDS and maximum GH peak levels were the strongest predictors. Weight and triceps skin fold thickness SDS and BA delay were other predictors. Growth velocity (cm/year) was positively correlated with triceps skin fold thickness and BA delay, and negatively correlated to height and weight SDS and maximum GH peak values. These factors represented 31% of variability of response with an error SD of 2.8 cm. In the 2nd year, the 1st year GV was the strongest predictor variable. Height, weight SDS and maximum GH values were the remaining predictive factors; with a positive correlation with 1st year GV and negatively correlated to GH peak values, height and weight SDS at onset. Predictive factors explained 62% of the variability of the response with an error SD of 1.8 cm.

In the 3rd year, growth response strongly correlated to GV of the preceding year and also to target height; these two predictive factors explained all the variability of the response (100% variability response). For the 4th year, no significant correlation was found between different variable and the 4th year growth response.

It was point of interest to observe that the longer the period of GH therapy, the lower variability of the prediction factors where the prediction factors explained 62 and 100% of the variability of the response in the 2nd and 3rd years compared to 31% in the 1st year. Moreover, it was also noted that for the period of catch up growth during the first two years of GH therapy, height and weight deficit, GH peak levels and BA delay were the main predictors; height and weight SDS, and GH peak values for the 1st and 2nd year, BA delay for the first year, and 1st year GV for the 2nd year. Past the period of catch up growth the numbers of predictive factors are less where the preceding year GV and target height were the main predictors.

It is important to mention that prediction model not only required to be of high predictive power (high r), but it is important also to be of high accuracy with low error SD. This low error SD is an important prerequisite if this model to be used as predictive tool for individual patient. In our data, the variability of factors in 2nd and 3rd years are lower and error SD is also smaller in the second year compared to 1st year which may improve their predictive utility.

It was obvious from the present work that during the period of catch up growth, coinciding with the 1st and 2nd years of GH therapy, the growth response is related to the degree of growth defect as expressed in height and weight deficit, BA delay and maximum GH peak values. Where during this catch up period, there was a negative correlation between growth velocity (cm/year) and height and weight SDS and GH peak values, and a positive correlation with BA delay; the lower the height and weight, and lower the GH peak values the higher the growth response, and the higher the BA delay the higher the growth response.

During the period of stable growth, past the 1st year of GH therapy, the preceding year GV was the most important predicting factor where the higher the recorded GV in the preceding year, the higher the GV in the 2nd and 3rd years. Moreover, during the period of stable growth (3rd year), target height was important predictor indicating that parental height not only determines height within the population[17] (Brook et al., 1977), but also the responsiveness to GH.

Moreover, in the same work we had the chance to develop an equation that describes the predicted height velocity for the first, 2nd and 3rd years of GH therapy.

For example, the height velocity (cm/year) in the first year of treatment = 11.35 + (-0.69 X height SDS) + (0.44 X weight SDS) + (0.64 X triceps skin fold thickness SDS) + (-0.04 X BA delay in years) + (-1.43 X In maximum GH) ± 2.8

Also, it was important to validate the accuracy of our

prediction method by comparing the predicted height using this model and the observed height velocity and calculating the residuals (prediction error) by subtraction of predicted height velocity from observed height velocity for each observation.

Non- significant statistical difference was found between observed and predicted height velocity in 1st year of GH therapy. Also the SDSs of the residuals for the first three years are small (0.91 cm for the first year, 0.78 cm for the 2nd year and very small SDS to be interpreted for the 3rd year).

Comparing our data with other studies ,reported that the first year GV SDS in 523 prepubertal patients with idiopathic GHD treated with GH was a function of age, body weight SDS, maximum GH response, MPH, injections frequency and GH dose. The overall variability was 40%, but the error SD was not given. [17] In the analysis of data base of 427 patients with idiopathic GHD **,** the first year height velocity was a function of age, height SDS MPH SDS, GH injection frequency, birth weight SDS, GH dose and weight for height index; these parameters explained 56% of the variability of the response with an error SD of 1.79 cm[18]. In study undertaken by KIGS [4] the first year growth response of 593 prepubertal patients with idiopathic GHD treated with GH they found that the model including the maximum GH response explained 61% of the variability of the response with error SD of 1.46 cm. The parameter of the natural log of the maximum GH response was the most important predictor; the greater the severity of GHD, the greater is the first year response. In addition, growth response was negatively correlated with CA and distance between child's height SDS and his MPH SDS. In the models excluding the maximum GH response to provocation testing, the factors explained 45% of the variability of the response with a SD error of 1.72 cm.

The most important single predictor was the difference between height SDS and MPH SDS. Otherwise, other predictors were identical. Also in the KIGS study 4 variables were found to be important for predicting 2nd, 3rd and 4th years growth response; height velocity during the previous year, body weight SDS, CA and weekly GH dose. The models for the 2nd and 3rd years explained 40% and 37% of the variability in the response with a SD error of 1.9 and 1.05 cm, respectively.

The most important predictor of response was the height velocity during the previous year. The model of the 4th year explained 30% of the variability in response with a SD error of 0.95 cm.

For the first year of GH therapy, height SDS, weight SDS, chronological age (CA) and bone age (BA) delay at onset, and maximum GH values were the strongest predictors. For the second year, first year growth velocity was the strongest predictor followed by the BA. For the third year, the strongest predictors were GV of 1st and 2nd years. For the 4th year, the strongest predictor factor was the 3rd year GV. For the period of catch up growth during the first two years of GH therapy, height and weight deficit, GH peak levels and BA delay were the main predictors. The prediction models presented in this study can be a useful tool for decisions about GH treatment of children with GHD

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