AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 2, Issue 7, 2024 ISSN (E): 2993-2149

Growth Response in Small for Gestational Age in Comparison with Growth Hormone Deficient Children within the First Year of Growth Hormone Treatment

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Abstract: Background: Growth hormone is used to treat short stature and growth failure associated with growth disorders. Growth parameters at birth and growth hormone status variably modulate response to growth hormone therapy.

Aim of the study: To compare growth response between short small for gestational age and growth hormone deficient children during the first year of growth hormone treatment and to see the differences between them at presentation regarding age and sex.

Patients and methods: Randomized controlled trials were done at the Endocrine and Diabetic Center in the Central Teaching Hospital of Pediatric in Baghdad City within the period started from Nov. 1, 2021, to the end of Nov. 2022. The study population was 100 short prepubertal children aged between 3–13 years, 50 patients diagnosed with growth hormone deficiency (GHD) and 50 with small for gestational age (SGA), and both were arranged for growth hormone (GH) treatment; GHD group was classified according to growth hormone level in the provocation test into severe GHD (max GH <3 ng/ml), and mild GHD (max GH 3-7 ng/ml). Both groups (GHD and SGA) were classified according to the average GH dose used during the first-year treatment into: [in GHD group low dose <= 0.03 (µg/kg. Day) and high dose > 0.03 (µg/kg. Day) and in SGA group into low dose <= 0.045 and high dose >0.045 (µg/kg. Day)] and see the growth response after six months and one year of treatment.

Main Outcome Measure: For each patient group, growth response parameters (height velocity and change in height standard deviation) during the first six months and one year of GH treatment were established.

Results: Responses to GH in terms of change in height standard deviation (ΔHt SDS) after one-year treatment were greatest in both groups (GHD and SGA) in age group =<5 years with p=0.0001, p=0.0001 respectively. Also, the height velocity (HV) was significantly better in the same age group in GHD patients with p=0.005. In the SGA group, there was greatest response with high dose GH (>0.045 µg/kg/day) in terms of HV and ΔHt SDS with (p=0.0001 and

p=0.006 respectively). Moreover, the response after one year of treatment in both groups were good response (ΔHt SDS >0.3), even in the SGA group but with a high dose of growth hormone. Also, as a comparison in HV between the two groups (GHD vs. SGA), the greatest response was in the GHD group with a significant P-value (p=0.002).

Conclusion: Younger age at diagnosis and treatment with growth hormone are associated with better response in ΔHt SDS and growth velocity for both small for gestational age and growth hormone deficient patients. High dose of growth hormone (>0.045µg/kg/day) is associated with better response in ΔHt SDS and growth velocity in the first-year treatment in SGA patients. In a comparison in response after one year of treatment with growth hormone between GHD and SGA children, the response to GH treatment was significantly better in the GHD group than in the SGA group in ΔHt SDS and growth velocity; moreover, both of them had a good response to GH after first-year treatment (ΔHt SDS >0.3).

Keywords: Growth, Gestational, Children, Shortness of stature, Patients.

Introduction

Shortness of stature (SS) is a prevalent condition among children, resulting from stunted linear growth. In statistical calculations, it is used to recalculate the height of children whose length is below the 97th percentile of their age- and sex-matched peers. If a person's height falls below the third percentile of their age and sex-related group, it is regarded as short stature[1].

One method of determining short stature is through the use of a growth velocity chart. This indicates that short stature is defined as a slow growth rate in a child, falling below the 25th percentile average velocity, which is less than the mean for that age group (graph [2,3,4]It is one of the critical health indicators in children. A continuous process occurring in biology, growth is dependent on a number of factors, including nutritional adequacy and hormonal balance [5,6]. It is of great importance to monitor the growth of children in preventive healthcare programmes for children. According to basic medical knowledge, any child suffering from illness will always be shorter in height [7]. Growth charts [8]can be used to map out what normal growth should be. This implies that the size of the newborn at delivery, in conjunction with the ageing process, determines the extent of growth and eventual adult height.

The early detection of shortness reduces the impact of any existing illness by minimising their adverse effects while increasing eventual adult body size. This challenge affects children worldwide but is more pronounced in less privileged areas. It remains hidden until much later, resulting in delayed growth outcomes[9].

The first step in preventing short stature is to understand its prevalence and the associated problems [10]. Short stature presents differently in different populations[11,12], with Bangladesh registering the highest rates at 73.6% during 1991 [13]. In the United States alone, approximately 2.2 million children aged under 18 have heights below this level [14]. The majority of cases are considered to be healthy, although a small number may have pathological causes of short stature. In 1995, Australia was the country with the lowest prevalence of short stature, with a percentage of 0%. When the growth plate fails, it may be due to a number of different abnormalities. These can involve non-uniform signalling from cells to other cells, which changes their behaviour. They can also involve substances that are produced by the cells and that collect in them for long periods instead of being given out, but not all at once, like in other tissues. Finally, they can involve molecular agents within the cell. Should complications arise, the result will be a chondrogenesis defect, which will result in the formation of tiny malformed bones. This will coexist with stature dwarfism, which is termed as skeletal dysplasia or chondrodysplasia, such as achondroplasia. [15,16,17]

Material and method

A randomised controlled trial was conducted at the Endocrine and Diabetic Center in Baghdad, involving 100 short prepubertal children aged 3-13 years. The participants were divided into two groups: 50 with growth hormone deficiency and 50 with small for gestational age. The patients were treated with growth hormones (Omnitrop and Nordiflex). The data from six months and one year were analysed.

The study analysed variables at diagnosis, including gender, birth weight, genetic background, and patient variables at the start of treatment. The study also analysed birth weight for gestational age to identify SGA children. GHD patients exhibited a peak GH concentration of ≤ 7 ng/ml in a provocation test and a low IGF-1 level. GHD patients were classified into two categories: those with severe GHD (peak GH response less than three ng/ml) and those with mild GHD (peak GH response between 3-7 ng/ml). During the course of treatment, the average GH dose was classified into two groups: low dose (≤ 0.03 µg/kg. Day) and high dose (> 0.03 µg/kg. Day) in the GHD group, and low dose (≤ 0.045 µg/kg. Day) in the SGA group. Ht and Ht SD were taken after six months and one year of GH treatment. First-year height velocity (HV) was calculated as the increment in height between the commencement of treatment and the subsequent measurement, which was conducted after a minimum of nine months and a maximum of 15 months of GH treatment.

The study employed the statistical software package SPSS-28 for data analysis, presenting the data in a series of simple measures, including frequency, percentage, mean, standard deviation, and range. Quantitative data was subjected to statistical testing using the Student's t-test, the paired t-test, or the analysis of variance (ANOVA), while qualitative data was tested using the Pearson chi-square test. A P-value of 0.05 or less was deemed statistically significant. Pearson's correlation coefficient was calculated to assess the linear relationship between two quantitative variables, with values ranging from -0.3 to >0.7.

Results

Fig 1- The distribution of children with GHD and SGA according to sex and age

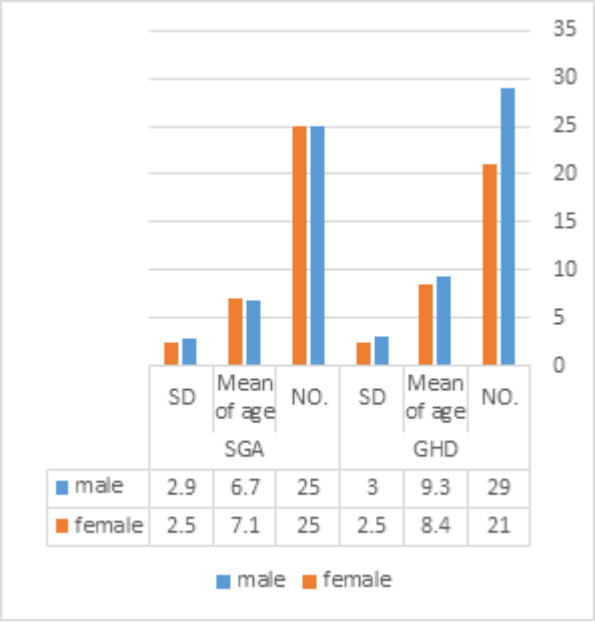

Table 2- Distribution and mean of age, sex, Ht SD, GH level, GH dose in GHD and SGA groups at diagnosis

		GH deficiency		SGA		P-value
		No	%	No	%	
Age (years)	<5y	3	6.0	13	26.0	0.002*
	5---9	20	40.0	25	50.0	

	=>10y	27	54.0	12	24.0	
	Mean ±SD (Range)	8.9±2.8 (3-13)		6.9±2.7 (3-13)		0.0001#
Gender	Male	29	58.0	25	50.0	0.422
	Female	21	42.0	25	50.0	
Mean Ht SD at diagnosis.		-2.72 ± 0.68		-3.24 ± 0.99		0.003#
GH level (ng/ml)	Severe (<3)	13	26.0	-	-	-
	Mild (3-7)	37	74.0	-	-	
GH dose (µg/kg/day)	=<0.03	30	60.0			
	>0.03	20	40.0			
	Mean ±SD	0.0313±0.0035				
GH dose (µg/kg/day)	=<0.045			19	38.0	
	>0.045			31	62.0	
	Mean ±SD			0.0482±0.0044		0.0001#

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

#Significant difference between two independent means using Students-t-test at 0.05 level.

#Significant difference between two dependent means using Paired-t-test at 0.05 level.

^Significant difference among more than two independent means using ANOVA-test at 0.05 level.

Table 3- The response to GH treatment according to age in both GHD and SGA groups

Response to GH in GHD	Age (years)			P-value
	=<5y	5---9	=>10y	
Δ Height SD after six months	0.77±0.12	0.25±0.21	0.18±0.26	0.001^
Δ Height SD after one year	1.27±0.31	0.51±0.33	0.45±0.31	0.0001^
Growth velocity	11.00±1.73	7.85±1.90	8.15±1.56	0.005^
Response to GH in SGA				
Δ Height SD after six months	0.47±0.16	0.15±0.27	0.13±0.14	0.0001^
Δ Height SD after one year	1.02±0.33	0.42±0.45	0.33±0.27	0.0001^
Growth velocity	7.92±2.60	7.20±2.25	7.33±1.97	0.647
P-value (GHD x SGA)	=<5y	5-9 years	=>10 years	
Δ Height SD after six months	0.009^	0.217	0.536	
Δ Height SD after one year	0.251	0.485	0.254	
Growth velocity	0.005^	0.309	0.204	

Table 4- The response to GH Tx according to the gender in both GHD and SGA groups

Response to GH in GHD	Gender		P-value
	Male	Female	
Δ Height SD after six months	0.29±0.26	0.17±0.27	0.117
Δ Height SD after one year	0.58±0.37	0.44±0.34	0.166
Growth velocity	9.07±1.96	8.29±1.71	0.148
Response to GH in SGA			
Δ Height SD after six months	0.26±0.26	0.19±0.26	0.354

Δ Height SD after one year	0.56±0.44	0.54±0.51	0.882
Growth velocity	7.84±2.08	7.00±2.40	0.192
P-value (GHD x SGA)	Male	Female	
Δ Height SD after six months	0.686	0.768	
Δ Height SD after one year	0.866	0.421	
Growth velocity	0.030#	0.046#	

Table 5- The response to GH Tx in the GHD group according to the level of GH deficiency.

Response to GH in GHD	GHD level (ng/ml)		P-value
	Severe (<3 ng/ml)	Mild (3-7 ng/ml)	
Δ Height SD after six months	0.21±0.27	0.25±0.27	0.600
Δ Height SD after one year	0.42±0.31	0.56±0.38	0.221
Growth velocity	8.54±1.45	8.81±2.03	0.658
-Data were presented as Mean±SD (Range)			
#Significant difference between two independent means using Students-t-test at 0.05 level.			

Table 7- a comparison in response to GH Tx between GHD and SGA groups according to changes in height SD and growth velocity.

Response to GH	GH deficiency	SGA	P-value
Δ Height SD after six months	0.24±0.27 (-0.50 - 0.90)	0.23±0.26 (-0.20 - 0.70)	0.813
Δ Height SD after one year	0.52±0.36 (-0.10 - 1.60)	0.55±0.47 (-0.20 - 1.60)	0.704
Growth velocity	8.74±1.88 (5.00 - 13.00)	7.42±2.26 (4.00 - 13.00)	0.002#
-Data were presented as Mean±SD (Range)			
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.			
#Significant difference between two independent means using Students-t-test at 0.05 level.			
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.			

Figure 2- Mean growth velocity in the GHD group during first year Tx with GH according to age, sex, level of GH deficiency, and GH dose.

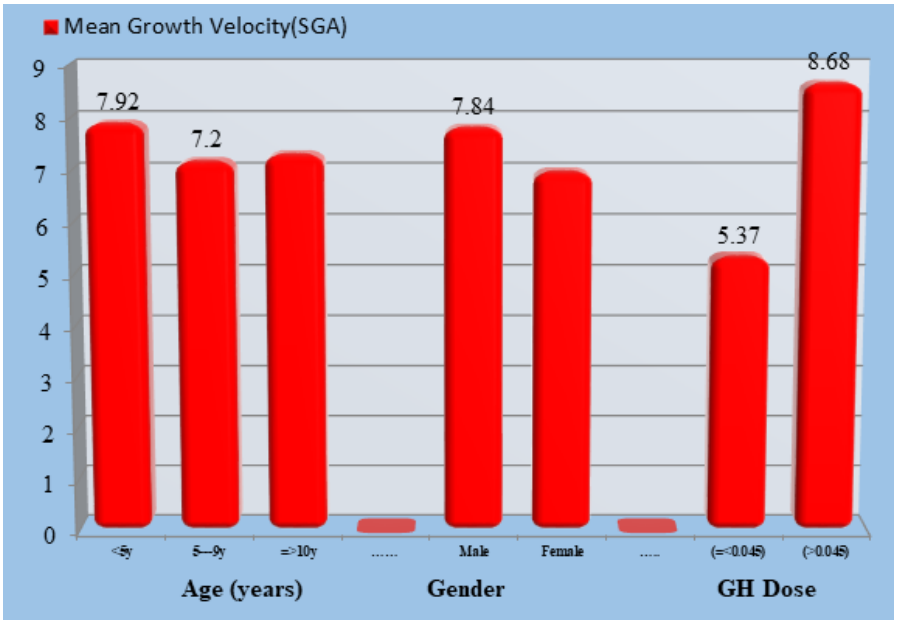

Table 8- The response to Tx in correlation to age and GH dose in the GHD group.

Gh deficiency		Age (years)	Gh dose (µg/kg/day)
Δ Height SD after six months	R	-0.287*	0.006
	P	0.043	0.968
Δ Height SD after one year	R	-0.324*	0.115
	P	0.022	0.428
Growth velocity	R	0.132	0.115
	P	0.362	0.425
*Correlation is significant at the 0.05 level. **correlation is highly significant at the 0.01 level.			

Table 9- The response to Tx in correlation to age and GH dose in the SGA group.

SGA		**Age (years)**	**GH dose** (µg/kg/day)
Δ Height SD after six months	R	-0.289*	0.339*
	P	0.042	0.016
Δ Height SD after one year	R	-0.366**	0.504**
	P	0.009	0.0001
Growth velocity	r	0.006	0.708**
	P	0.969	0.0001
*Correlation is significant at the 0.05 level. **Correlation is highly significant at the 0.01 level.			

Discussion

This study's findings support Ranke and Lindberg (78) rather than Straetemans et al. (89) regarding the SGA group, which may be due to the fact that SGA patients tend to be shorter and stockier, which prompts their loved ones to seek medical advice and prompts a diagnosis at an earlier age than in the GHD group.

Furthermore, it was found that the males in the SGA group were diagnosed at a younger age, which is in agreement with Straetemans et al. (89). This finding could be indicative of a gender-specific pattern in our demographic where girls are typically diagnosed later than boys. [17,18]

This study confirmed the findings of Straetemans et al. that there was a statistically significant difference in the amount of height affection between the SGA and GHD groups at diagnosis. This could be due to the fact that GHD patients may have a partial GH deficiency with a normal response to growth plate GH, in contrast to SGA patients who had GH resistance at the growth plate[19,20].

Consistent with previous research showing a negative correlation between age at treatment initiation and response to GH in the first year of therapy (Clayton et al., 2017; Chatelain et al., 1990; SGA group), this study also demonstrated that starting therapy (GH treatment) earlier is more effective than delaying therapy.

This finding is in line with Chatelain et al. (90) and is similar to the one in the GHD group, where there is a significant difference in the effect size depending on when therapy began. This could be because, as children enter puberty, their average HV drops, and the correlation between starting treatment early and a larger effect size could be due to the smaller height deficit in younger children compared to older ones.

It is possible that the small sample size of 13 patients with severe GHD is to blame for this study's inability to detect higher levels of HV and ΔHt SDS during the first year of treatment compared to the mild deficiency group. This contradicts the findings of Ranke and Lindberg and Straetemans et al. (89), who discovered a better response with severe GHD than mild. This could be due to the upregulation of GH receptors in severe GHD, leading to a greater response to GH therapy.

According to Ranke and Lindberg and Straetemans et al. [21], there was no discernible difference in response between the high and low doses of GH in the GHD group, but after one year of treatment, there was a significant difference in the SGA group when it came to the high dose of GH in HV and ΔHt SDS. Since a type of GH resistance exists in SGA children, requiring a greater dosage for a better response, this agrees with Chatelain et al. [22]and Ranke and Lindberg, where Ranke and Lindberg and Straetemans et al. found similar results regarding the overall response in HV between the two groups after the first year of treatment; however, hormonal resistance in SGA patients may explain why the GHD group had a better response.

Conclusion

The study revealed that a younger age at diagnosis and treatment with growth hormone are linked to a more favorable response in ΔHt SDS (standard deviation score) and growth velocity for both patients who are short for gestational age and those who have a growth hormone deficiency. Administering high dosages of growth hormone (>0.045µg/kg/day) resulted in a more favorable response during the initial year of treatment in patients with small for gestational age (SGA) condition. After one year of treatment, the GHD group had a significantly superior response in ΔHt SDS (standard deviation score) and development velocity.

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