Original Paper

Final Height in Children with Idiopathic Growth Hormone Deficiency treated with Growth Hormone: Albanian experience

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ABSTRACT: Objective- To evaluate the efficiency of recombinant growth hormone for increasing adult height in children treated for idiopathic growth hormone deficiency and to evaluate the prognostic factor for height at the end of treatment. **Design-** Observational follow up study. **Setting-** Population based registry. **Participants-** All Albanian children diagnosed with idiopathic growth hormone deficiency who had attained final height. Their treatment started between 2001 and 2011. **Main outcome measures-** Annual changes in height, and change in height between the start of treatment and adulthood; the importance of the factors that influence on final height. **Results-** Adult height was obtained for 83 (55%) patients. The mean dose of growth hormone at start of treatment was 0.21 IU/kg/week for 29 patients and 0.24 IU/week for 54 patients. Height gain was 2.41±1.19 z-scores, resulting in an adult height of -1.98±1.12 z-score (girls, -2.05±1.27 z-score; boys, -1.95±1.20 z-score). Patients who completed the treatment gained 2.40±1.13 z-score of height in 4.0±2.0 years. Most of the variation in height gain was explained by regression towards the mean, patients' characteristics, and delay in starting puberty. **Conclusion-** Nearly all our patients with idiopathic growth hormone deficiency treated with growth hormone were able to achieve their genetic height potential. Despite starting treatment late, they managed to gain 2.40±1.13 HAZ score in height and the final height for majority of them (61.5%) was within the target height range. It was found that the final height had good correlation with the prediction height, HAZ score at beginning of treatment, change of HAZ score during the puberty, duration of treatment with GH, and pubertal stage at the start of therapy.

KEYWORDS: *Idiopathic Growth Hormone Deficiency, HAZ (Height for Age Z-score), Final height, Growth hormone therapy*

Introduction

Growth hormone has been used in the treatment of short stature since 1957 [1]. Prior to 1985, human cadaver-derived pituitary growth hormone was used. Recombinant human growth hormone which was approved in 1985 made available a reliable, virtually unlimited resource [2] to replace human pituitary growth hormone (which was withdrawn due to reported cases of Creutzfeldt-Jakob disease). Idiopathic growth hormone deficiency is the main indication for treatment in more than one half of children receiving growth hormone therapy [3].Growth hormone therapy aims to normalize growth and help these patients achieve final height within their genetic potential and the normal range for the general population. Long term studies had shown that it was possible to achieve the above objectives in patients who were optimally treated [4, 5]. In Albania, the use of growth hormone has been increasing slowly since 2001 due to extreme high cost of treatment, lack of funding for patients and lack of public awareness until recently. Moreover, data regarding response to treatment and factors affecting final height in our local population have not been available. This study aims to evaluate the final height outcome among the Albanian children diagnosed with idiopathic growth hormone deficiency treated with recombinant human growth hormone.

Materials and Methods

This is a register based cohort study. The medical records of all patients who were on growth hormone therapy from January 2001 in the Pediatric Endocrine Unit, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania were reviewed. Only patients with idiopathic growth hormone deficiency [isolated (IGHD) or multiple pituitary hormone deficiencies (MPHD)] who had attained final height till January 2013 were included in this study. Patients with syndrome/tumors/other systemic diseases were excluded. (Fig. 1).

The diagnosis of idiopathic growth hormone deficiency was defined based on the fulfillment of both the auxological and biochemical criteria.

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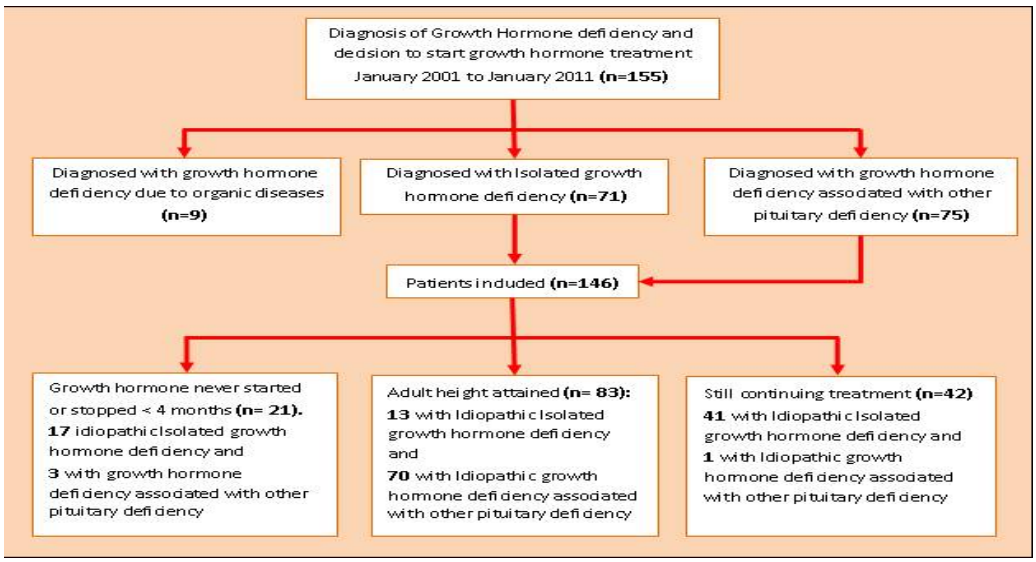

Fig.1. Flow chart of study methodology

For auxological criteria, patient was short (height less than -2 Z-score), slowly growing with poor height velocity for age less than 6cm/year (for patients ≤ 3 years old) or less than 4cm/year (for patients > 3 years old) and a delayed bone age (more than 2 years). Biochemically the stimulated peak growth hormone level was less than 10 mU/L in two separate growth hormone stimulation tests. Growth hormone level was measured by the ICMA in our centre. Prepubertal children were primed with sex steroid before the growth hormone stimulation test. The following data were retrieved from patients' medical record: gender, diagnosis, mid parental height, chronological age, bone age and height at starting treatment, height after first year of treatment, age and height at onset of puberty, age of attaining final height and final height, duration of growth hormone treatment and mean growth hormone dose. Height of patients were plotted using the WHO growth charts and were standardized by calculating their height SDS (Z-score) [6]. Onset of puberty was defined by achievement of testicular volume of 4 mls or more in boys or breast stage 2 in girls [7]. Bone age was calculated by reading the plain radiograph of left hand and wrist using the Greulich and Pyle atlas [8] by a single observer. Bone age deficit was defined as (chronological age) – (bone age). Mid parental height was defined by using Tanner's method [9]. Mid parental height for boys (cm) = (father's height + mother's height + 13)/2; mid parental height for girls (cm) = (father's height + mother's height - 13)/2. Target height range = mid parental height +/- 6.5cm. Final height was defined as height reached when growth velocity was less than 2cm/year calculated over a minimum of 9 months where the chronological age was more than 17 years or bone age more than 16 years in boys and chronological age more than 16 years or bone age more than 15 years in girls [10]. Mid parental height, and final height were then standardized by calculating their height SDS (Z-score) using the WHO growth charts (Anthro and Anthro_plus 2007). Results were expressed as mean ± standard deviation (SD). Data was analyzed using the IMB SPSS Statistics Version 20. Pearson correlation analysis was performed on the data in order to analyze the relationship between various parameters with final height SDS. A p value < 0.05 was considered as statistically significant.

Results

Characteristics of participants at baseline and treatments

83 patients, who were treated with growth hormone, had attained adult height. The male: female ratio was 64: 19. 15.6% (13/83) of them had isolated growth hormone deficiency while 84.4% (70/83) had multiple pituitary hormone deficiencies. The mean age of starting GH treatment in our patients was 13.34±2.6 years old, with boys starting treatment later (13.46±2.45years old) compared to girls (12.91±2.92years old). The mean bone age deficit was 5.25±1.90 years. This had resulted in severe height deficit by -4.39±1.05 z-score at start of treatment. The mean mid parental height was -1.02±1.12 z-score. 14.5% (12/83) were in puberty in the beginning of the GH therapy. 85.5% (71/83) began the puberty after the

therapy started. 45.1% (32/71) had spontaneous puberty while in the remaining 54.9% (39/71) the puberty was inducted. The mean age of spontaneous puberty was 12.84±1.39 years while; the mean age of induced puberty was 15.13±1.04 years. Overall, the mean age of puberty was 14.11± 1.66 years old with males attaining puberty later (14.36±1.54 years old) compared to girls (13.09± 1.77 years old).

The mean duration of growth hormone treatment was 3.99±1.97 years and the average GH dose was 0.23 mg/kg/week. (Table1).

Table 1

		IGHD	MPHD	Total
Gender	Female (nr.)	4	15	19
	Male (nr.)	9	55	64
Age at starting treatment (years)		11.9±3.3	13.6±2.3	13.3±2.6
HAZ score at start of treatment		-4.69±1.18	-4.33±1.02	-4.39±1.05
Bone age deficit(years)		5.1±1.8	5.3±1.9	5.2±1.9
Mid Parental HAZ score		-1.2±1.1	-1.0±1.1	-1.0±1.1
HAZ score at onset of puberty		-3.92±1.71	-3.62±1.21	-3.68±1.31
Pubertal HAZ gain*		1.88±0.94	1.53±0.86	1.81±0.93
HAZ score at the end of treatment (Final HAZ score)		-2.15±0.99	-1.94±1.25	-1.98±1.21
HAZ score gain from start to the end of treatment**		2.31±0.75	2.41±1.19	2.40±1.13
Duration of treatment (years)		4.54±2.14	3.89±1.93	3.99±1.97
GH dose	0.245 mg/kg/ week (nr.)	10	44	54
	0.21 mg/kg/ week (nr.)	3	26	29

Pubertal HAZ gain = (Final HAZ score) – (HAZ score at onset of puberty)
****HAZ score gain from start to the end of treatment = (Final HAZ score) – (HAZ score at start of treatment)***

Changes in height

After one year of treatment, almost all patients gained 0.951±0.67 z-score in height.

The mean height SDS at onset of puberty was -3.68±1.31 z-score and our patients gained average 1.81±0.93 z-score during puberty. When the treatment was completed, the height gain was 2.40±1.13 z-score with the mean final height SDS -1.98±1.21 z-score. They stopped the treatment around the mean age of 17.34±1.34 years old. Most of the height was gained during the first six years (Table 2).

Table 2

	Diagnosis				**One-Sample Test** 95% Confidence Interval of the Difference	
	IGHD	MPHD	Total			
	Mean±SD	Mean±SD	Mean±SD	N	t	Sig. (2-tailed)
HAZ_change_year_1	1.08±0.28	0.94±0.51	0.96±0.48	83	18.295	.000
HAZ_change_year_2	0.25±0.45	0.62±0.49	0.56±0.50	78	9.982	.000
HAZ_change_year_3	0.42±0.51	0.42±0.53	0.42±0.53	69	6.638	.000
HAZ_change_year_4	0.50±0.53	0.43±0.50	0.44±0.50	54	6.512	.000
HAZ_change_year_5	0.33±0.50	0.45±0.57	0.42±0.55	38	4.704	.000
HAZ_change_year_6	0.00±0.00	0.43±0.51	0.32±0.48	19	2.882	.010
HAZ_change_year_7	0.00±0.00	0.30±0.48	0.25±0.45	12	1.915	.082
HAZ_change_year_8	0.00±0.00	0.00±0.00	0.00±0.00	7	.	.
HAZ_change_year_9	0.00±0.00	0.00±0.00	0.00±0.00	3	.	.

Table 3

		Total height gain (cm)	**Height velocity (cm/year)**
		Mean±SD	Mean±SD
IGHD	Female	34.25±17.17	6.72±1.07
	Male	37.78±14.70	8.99±1.92
	Total	36.69±14.85	8.29±1.98
MPHD	Female	26.73±15.77	7.62±1.53
	Male	34.31±14.99	8.91±1.99
	Total	32.69±15.37	8.64±1.97
Total	Female	28.32±15.89	7.43±1.47
	Male	34.80±14.89	8.92±1.97
	Total	33.31±15.27	8.58±1.96

The mean of total height gain and annual growth velocity was estimated by group-diagnosis and gender (Table 3). Male patients had greater total height gain and higher height velocity too compared to girls. Patients with IGHD had greater height gain, but slower height velocity compared to MPHD patients.

The fastest growth velocity was during the first year of treatment (11.37±3.25 cm/year), and started getting reduced from year to year. After 8 years of treatment, growth velocity became

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insufficient, but this is due to age of patients and their bone ages which were in the upper limit and conditioned the end of the height growth (Table 4).

Table 4

Group Statistics					One-Sample Test	
	Gender	N	Mean±SD	Total	t	Sig. (2-tailed)
Height_velocity_year_1	F	19	10.16±3.70	11.37±3.25	31.858	.000
	M	64	11.73±3.04			
Height_velocity_year_2	F	16	7.31±1.66	7.76±2.50	27.313	.000
	M	62	7.87±2.68			
Height_velocity_year_3	F	14	6.86±3.11	6.67±2.85	19.378	.000
	M	55	6.62±2.81			
Height_velocity_year_4	F	12	5.00±2.95	5.63±3.07	14.064	.000
	M	47	5.79±3.11			
Height_velocity_year_5	F	9	5.22±3.38	5.90±3.10	11.874	.000
	M	30	6.10±3.04			
Height_velocity_year_6	F	4	5.00±2.94	5.52±3.04	8.318	.000
	M	17	5.65±3.14			
Height_velocity_year_7	F	3	3.33±2.88	5.25±2.83	6.421	.000
	M	9	5.89±2.66			
Height_velocity_year_8	F	2	0.00±0.00	2.71±2.62	2.733	.034
	M	5	3.80±2.28			
Height_velocity_year_9	F	0a	0.00 ±0.00	2.00±0.00		
	M	2	2.00±0.00			

Table 5

Correlations		
		Final_Height
	Pearson C.	Sig. (2-tailed)
Mid_Parental_Height	.29439	.00000
HAZ_at_start_of_treatment	.44528	.00002
HAZ_change_by_puberty_start	.37188**	.00141
Duration_of_treatment	.41116**	.00011
HAZ_before_puberty	.53403	.00000
Pubertar_stade_in_start_of_GH	-.21888	.04681
Dose_of_GH	.19278	.08079

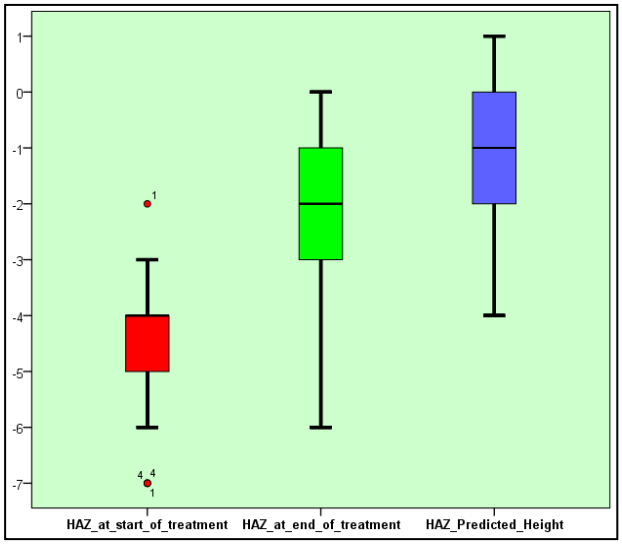

Fig.2.

When we performed the Pearson correlation analysis between final heights SDS and various parameters listed in Table 5, we found that only 6 variables were correlated with the final height outcome in our patients, i.e. mid Parental Height, height z-score at start of treatment, height z-score at onset of puberty, HAZ score change during the puberty, duration of treatment, HAZ score before onset of puberty and pubertal stage in start of GH.

Other variables such as bone age in start of treatment, bone age deficit and growth hormone dose were not statistically related to the final height outcome in our patients.

51 out of 83 patients (61.5%) achieved their genetic height potential with the final height corrected for mid parental height [(final height SDS) – (mid parental height SDS)] being within the target height range (Fig.2).

Predictive models for adult height

Growth is a multi-factorial process and baseline differences between patient treatments complicate comparison. Therefore, we constructed Regression of Automatic Linear Modeling with factors explaining adult height. The importance of main predictors on the target (final height) is presented in the Fig.3.

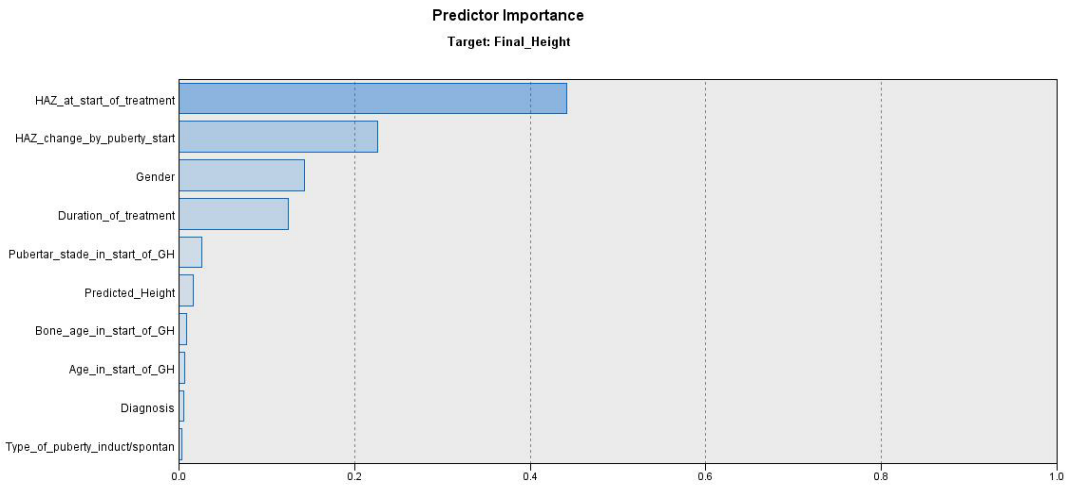

Fig.3.

In the final model, variables determined at baseline that predicted a good outcome were HAZ score at start of treatment(44.2%) , HAZ score changes during puberty(22.4%), gender (14.3%), duration of treatment(12.4%), and prepubertal status (2.6%) (Fig.4 and Table 6).

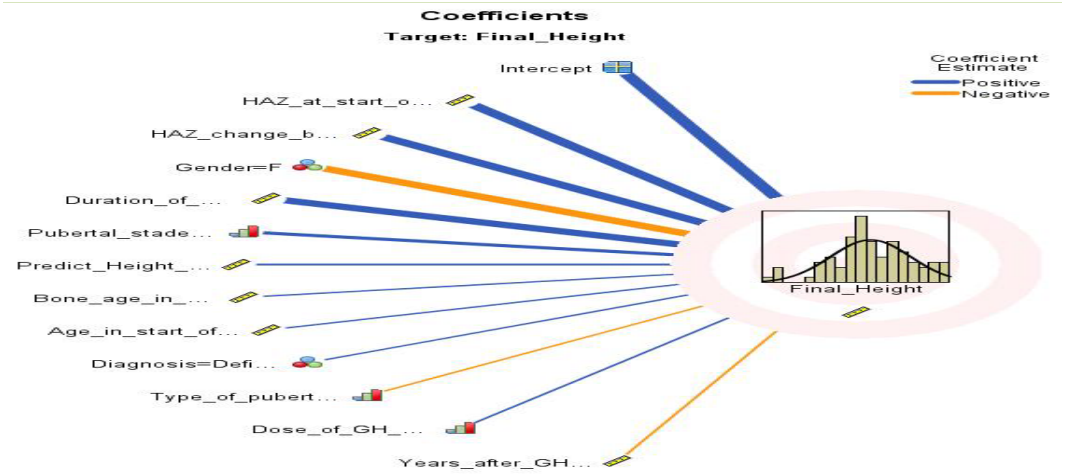

Fig.4

Thus, younger patients presenting no signs of puberty and with marked bone age delay had better outcomes (p- value 0.035). A negative association with female sex reflected sex dependent differences in pubertal age. The duration of treatment was positively associated with final height. Growth hormone dose did not predict adult height. Together, all variables associated with treatment accounted for 10.02% (Intercept significance 0.0000) of outcome (Target Height).

Table 6

					95% Confidence Interval		
Model Term	Coefficient	Std. Error	t	Sig.	Lower	Upper	Importance
Intercept	**121.97**	**20.41**	**5.97**	**0.0000**	**81.24**	**162.70**	
HAZ_at_start_of_treatment	6.31	0.64	8.26	0.0000	4.03	6.60	**0.442**
HAZ_change_by_puberty	5.67	0.96	5.89	0.0000	3.75	7.59	**0.226**
Gender_female	-8.49	1.81	-4.69	0.0000	-12.11	-4.88	**0.143**
Duration_of_treatment	3.29	0.75	4.38	0.0000	1.79	4.79	**0.124**
Pubertar_stade_in_start_of_GH	3.92	1.96	2.00	0.049	0.01	7.83	**0.026**

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Discussion

The above study reflected our experiences in using recombinant human growth hormone in patients with idiopathic growth hormone deficiency. The mean age of starting treatment in our patients was 13.34±2.6 years old which was actually older compared to study done by Westphal *et al* 4 but comparable to earlier studies published in late 90's and early 2000 [10,11,12,13].

As a result of this, our patients had extreme short stature at start of treatment with mean height

-4.4±1.0 z-score. The short duration of treatment before onset of puberty also resulted in insufficient increase in prepubertal height with the mean height at onset of puberty still being

-3.68±1.31 z-score. With an impressive gain of 0.951±0.67 z-score within first year of treatment and total HAZ score change from starting treatment with 2.40±1.13 z-score, 61.5% of our patients achieved their final height within the target height range.

The mean pubertal height gain was 1.81±0.93 z-score which was compared to study by August GP et al [13] but higher to studies by Westphal et al [4]. However the lower final height z-score achieved compared to results from Westphal et al, might be explained by the earlier age of attaining final height in our patients (17.34±1.34 years vs 18 years), and shorter duration of treatment (3.99±1.97 years vs 8.5 years) in our cohort study .

Earlier published studies regarding the final height outcome in patients with idiopathic growth hormone deficiency had somehow shown conflicting results. Some studies reported that although growth hormone therapy produced significant height gain, it failed to produce consistent attainment of full genetic potential which may be due to suboptimal dosing and shorter duration of treatment [11, 12, 13]. However many studies concluded that given optimal treatment, patients with idiopathic growth hormone deficiency may achieve their genetic potential [4,5,7,10]. In regards to our results, they were similar to those reported in earlier studies where it was possible to achieve final height within the target height range but absolute final height remained at the lower end of normal for the majority of our patients and full genetic potential was not always achieved for all patients.

Correlation analysis showed that only 6 variables were significantly related to the final height outcome in our patients i.e. mid Parental Height, height z-score at start of treatment, height z-score at onset of puberty, HAZ score change during the puberty, duration of treatment, HAZ score before onset of puberty and pubertal stage in start of GH. Mid Parental Height z-score had the greatest influence on final height. This was obvious, as the final height achieved would depend on height of both parents. Similar findings had also been reported previously [7,10,14]. Older age of starting treatment among our patients had caused a narrow window period for treatment. Therefore, those with severe height deficit at the start of treatment and at the onset of puberty would be shorter adults.

Even though the age of starting treatment was not significantly correlated, the duration of the treatment correlated was correlated positively with the final height outcome in our patients. Ranke *et al* [15] reported that in patients who started treatment less than 3 years of age compared to those who started treatment between 7 to 8 years old, there was higher responsiveness to treatment i.e. greater gain in height per growth hormone dose unit in the very young compared to the older children. Therefore, early diagnosis and initiation of treatment is determinant to the final height outcome. This prevents severe height deficit at the start of the treatment and allow opportunity for these children to catch up as much as growth before puberty [13,16]. It is obvious now that the most successful strategies for enhancing growth hormone induced growth must concentrate on growth during early childhood [5]. However for adolescents with growth hormone deficiency who were most growth retarded at the start of puberty, higher growth hormone dose had been shown to increase final height z-score without increasing the rate of skeletal maturation [17]. Even though smaller growth hormone dose had been used in our patients, growth hormone dose was not related to the final height outcome. Similar finding had also been reported by Carel JC *et al.* [12]. Our study was limited by its small sample size, which was due to small number of treated patients who had attained final height. Despite the relatively small number of children in the study, Automatic Linear Regression model was built to assess the importance of the variable on the final height. This model noted out that HAZ score at start of treatment, HAZ score changes

during puberty, gender, duration of treatment, and prepubertal affects strongly on final height.

Conclusion

Nearly all our patients with idiopathic growth hormone deficiency treated with growth hormone able to achieve their genetic height potential. Despite starting treatment late, they managed to gain 2.40±1.13 HAZ score in height and the final height for majority of them (61.5%) was within the target height range. This study highlighted the importance for early diagnosis and treatment in children with growth hormone deficiency. This is to ensure adequate duration of treatment to optimize the prepubertal growth so that height prognosis of these children can be further improved.

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