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International Journal of Current Research
Vol. 7, Issue, 02, pp.12495-12499, February, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

IDIOPATHIC ISOLATE GROWTH HORMONE DEFICIENCY TREATED WITH GROWTH HORMONE: ALBANIAN EXPERIENCE

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ARTICLE INFO

Article History:
Received 17th December, 2014
Received in revised form
19th January, 2015
Accepted 21st January, 2015
Published online 26th February, 2015

Key words:

Idiopatic isolated Growth Hormone Deficiency (IGHD),
HAZ (Height for Age Z-score),
Final height,
Growth hormone Therapy.

ABSTRACT

Objective: To evaluate the efficacy of recombinant growth hormone for increasing adult height in children treated for idiopathic isolated growth hormone deficiency (IGHD).
Design: Observational follow up study.
Setting: Population based registry.
Participants: All Albanian children diagnosed with idiopathic isolated growth hormone deficiency and 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.
Results: 71 patients were diagnosed with idiopathic isolated growth hormone in the period mention above. Adult height was obtained for 13 (13.3%) patients. The male: female ratio was 9:4. HAZ score at the start of treatment was -4.69±1.18. The mean dose of growth hormone at start of treatment was 0.21 IU/kg/week for 3 patients and 0.24 IU/week for 10 patients. Height gain was 2.31±0.75 z-scores, resulting in an adult height of -2.15±0.99 z-score (girls, -2.25±1.50 z-score; boys, -2.11±0.78 z-score). Patients who completed the treatment gained 2.31±0.75 z-score of height in 4.54±2.14 years.
Conclusion 69.2% our patients with idiopathic isolated growth hormone deficiency treated with growth hormone able to achieve their genetic height potential. Despite starting treatment late, they managed to gain 2.31±0.75 HAZ score in height and the final height for majority of them 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.

INTRODUCTION

Growth hormone has been used in the treatment of short stature since 1957 (**Raben, 1957**). 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 (**Hardin *et al.*, 2007**) 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 (**Gary Butler, 2007**). 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 (**Westphal and Lindberg, 2008; Reiter *et al.*, 2006**). 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 isolated idiopathic growth hormone deficiency treated with recombinant human growth hormone.

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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 isolated growth

hormone deficiency (IGHD) who had attained final height were included in this study. Patients with syndrome, tumors, other systemic diseases and growth hormone deficiency associated with other pituitary deficiency were excluded (Fig. 1).

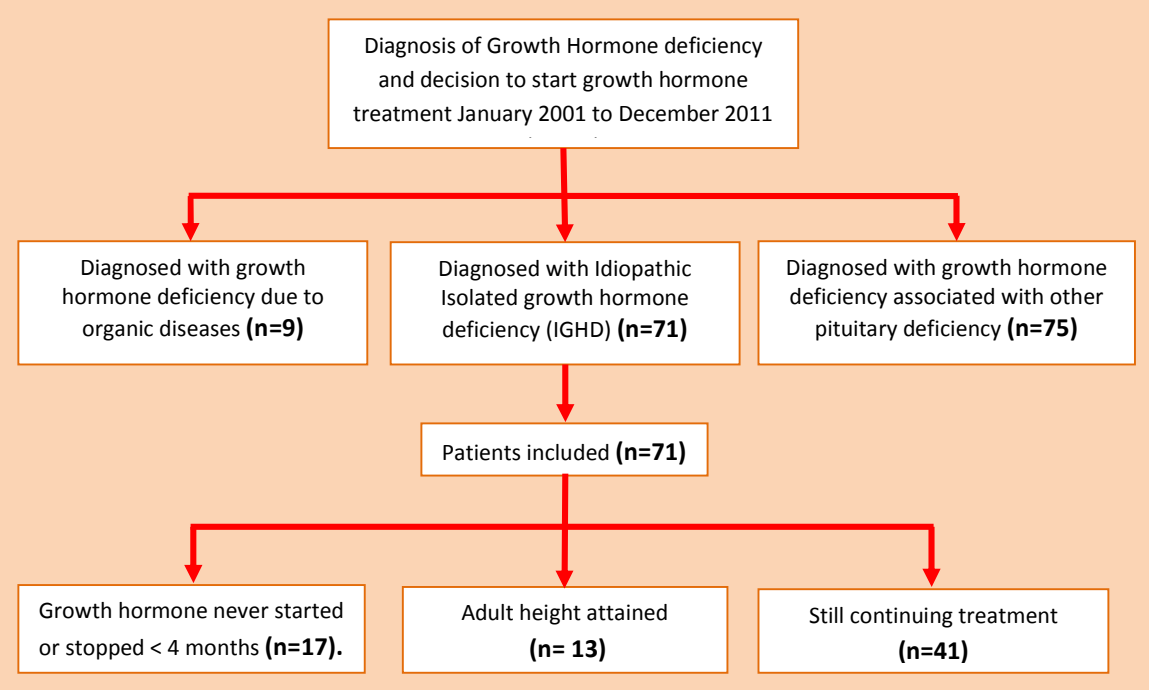


Fig. 1. Flow chart of study methodology

The diagnosis of isolated idiopathic growth hormone deficiency was defined based on the fulfillment of both the axiological and biochemical criteria. For axiological 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 10mU/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) (http://www.who.int/childgrowth/software/en/). Onset of puberty was defined by achievement of testicular volume of 4 mls or more in boys or breast stage 2 in girls (**Thomas *et al.*, 2001**). Bone age was calculated by reading the plain radiograph of left hand and wrist using the Greulich and Pyle atlas (**Radiographic Atlas of Skeletal Development of the Hand and Wrist, 1959**) by a single observer. Bone age deficit was defined as (chronological age) – (bone age). Mid parental height (MPH) was defined by using Tanner's method (**Tanner *et al.*, 1950**). 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 (**Cutfield *et al.*, 1999**). 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 Version20. 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

13 patients, who were treated with growth hormone, had attained adult height. The male: female ratio was 9:4. The mean age of starting GH treatment in our patients was 11.9±3.3 years old with boys starting treatment later (13.66±2.32years old) compared to girls (13, 38±2.50 years old). The mean bone age deficit was 5.1±1.8years. This had resulted in severe height deficit of -4.69±1.18z-score at start of treatment. The mean mid parental height was -1.2±1.1 z-score. 100% (13/13) began the puberty after the therapy started. 61.5% (8/13) had spontaneous puberty while in the remaining 38.5% (5/13) the puberty was inducted. The mean age of spontaneous puberty was 12.48±1.74 years while, the mean age of induced puberty was 15.20±1.06 years. Overall, the mean age of puberty was 13.53±2.01 years old with males attaining puberty later

(13.75±1.89years old) compared to girls (13.02± 2.47 years old) (p-value 0.57). The mean duration of growth hormone treatment was 4.54±2.14 years and the average GH dose was 0.235 mg/kg/week (Table1).

Table 1. Clinical characteristics of patients with Idiopathic IGHD treated with recombinant human GH

	Male	Female	Total
Nr.	4	9	13
Age at starting treatment (years)	12.3±3.03	11.15±4.1	11.93±3.26
HAZ score at start of treatment	-4.67±1.0	-4.75±1.71	-4.69±1.18
Bone age deficit(years)	5.61±1.50	3.89±2.05	5.1±1.8
Mid Parental HAZ score	-1.33±1.12	-0.75±1.26	-1.2±1.1
HAZ score at onset of puberty	-4.11±1.69	-3,50±1.91	-3.92±1.71
Pubertal HAZ gain*	1.59±0.89	1.38±0.90	1.88±0.94
HAZ score at the end of treatment (Final HAZ score)	-2.11±0.78	-2.25±1.50	-2.15±0.99
HAZ score gain from start to the end of treatment**	2.22±0.83	2.50±0.58	2.31±0.75
Duration of treatment (years)	4.33±2.06	5.0±2.58	4.54±2.14
GH dose 0.245 mg/kg/ week (nr.)	3	7	10
0.21 mg/kg/ week (nr.)	1	2	3

***Pubertal HAZ gain = (Final HAZ score) – (HAZscore 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 gained1.08±0.28 z-score in height.

Table 2. Height gained during treatment (based on years of treatment)

	Nr.	Mean±SD	Corr.	Sig.
HAZ_change_year_1	13	1.08±0.28	.972	.000
HAZ_change_year_2	12	0.25±0.45	.886	.000
HAZ_change_year_3	10	0.42±0.51	.781	.008
HAZ_change_year_4	9	0.50±0.53	.783	.013
HAZ_change_year_5	6	0.33±0.50	.500	.667
HAZ_change_year_6	3	.00±.00	.	.
HAZ_change_year_7	2	.00±.00	.	.
HAZ_change_year_8	1	.00±.00	.	.

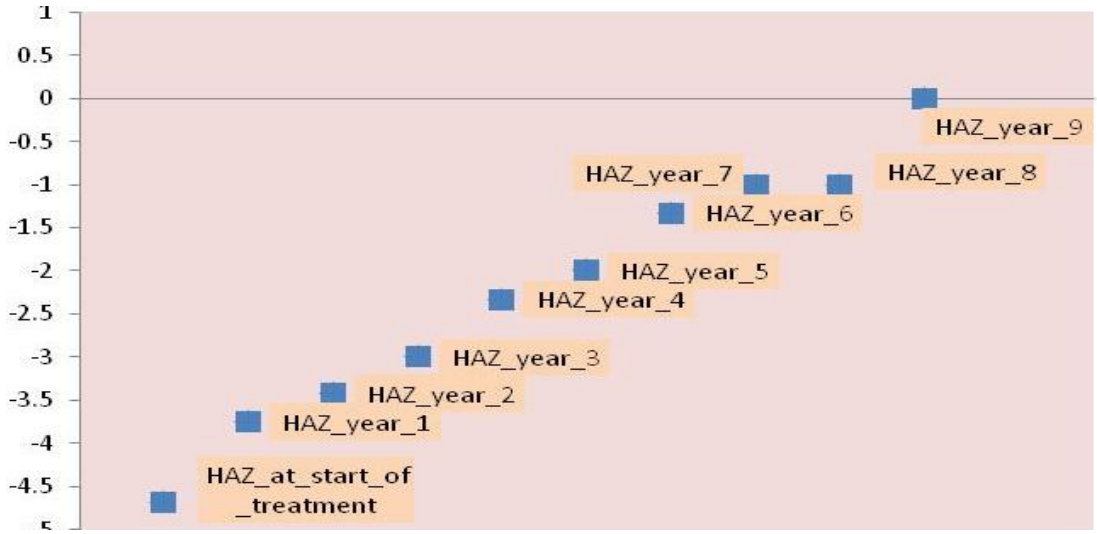
The mean height z-score at onset of puberty was -3.92±1.71z-score and our patients gained average 1.88±0.94 z-score during puberty. When the treatment was completed, the height gain was 2.31±0.75 z-score with the mean final height -2.15±0.99 z-score. They stopped the treatment around the mean age of 16.60±1.79 years old (boys' 16.80±1.70 years and girls' 16.20±2.19 years) (p-value 0.61). Most of the height was gained during the first four years (Table 2 and Graphic 1).

The mean of total height gain was 36.69±14.85 cm, and annual growth velocity was 8.29±1.98 (cm/year). Male patients had greater total height gain (37.78±14.70cm vs. 34.25±17.17 cm) and higher height velocity too (8.99±1.92 cm/yr vs. 6.72±1.07 cm/yr) compared to girls (Table 3).

When we performed Pearson correlation analysis between HAZ score at the end of treatment (Final HAZ score) with various parameters listed in Table 4, we found that only 6 variables were good correlated with the final HAZ outcome in our patients, i.e. age at the start of treatment, height z-score at start of treatment, HAZ score change by puberty, duration of treatment, HAZ score before onset of puberty and bone age deficit. Other variables such as growth hormone dose and mid parental HAZ score were not statistically related to the final height outcome in our patients. 9 out of 13 patients (69.2%) 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 (Graphic 2)

DISCUSSION

The above study reflected our experiences in using recombinant human growth hormone in patients with idiopathic isolated growth hormone deficiency. The mean age of starting treatment in our patients was 11.9±3.3 years old which was actually older compared to study done by **Westphal *et al.* (2008)** but comparable to earlier studies published in late 90's and early 2000 (**Cutfield *et al.*, 1999; Guyda, 1999; Carel *et al.*, 2002; August *et al.*, 2011**).



Graphic 1 Height gained (HAZ) during treatment

As a result of this, our patients had extreme short stature at start of treatment with mean height -4.69±1.18 z-score. The short duration of treatment before onset of puberty also resulted in

insufficient increase in prepubertal height with the mean height SDS at onset of puberty still -3.92±1.71 z-score.

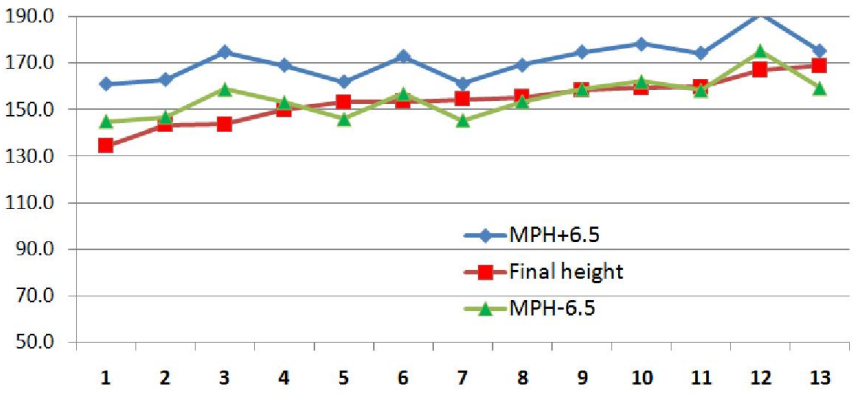
2008) might be explained by earlier age of attaining final height in our patients

Table 3. Height velocity based on years of treatment and on gender

Group Statistics				
	Gender	N	Mean±SD	Total (Mean±SD)
Height_velocity_year_1 (cm/year)	Female	4	9.75±1.708	11,23±2.31
	Male	9	11.89±2.315	
Height_velocity_year_2 (cm/year)	Female	4	7.00±0.816	7,25±1.42
	Male	8	7.38±1.685	
Height_velocity_year_3 (cm/year)	Female	4	5.75±4.031	6,25±3.02
	Male	8	6.50±2.673	
Height_velocity_year_4 (cm/year)	Female	3	5.67±2.517	7,10±3.78
	Male	7	7.71±4.231	
Height_velocity_year_5 (cm/year)	Female	3	6.00±5.000	5,50±3.06
	Male	7	5.29±2.360	
Height_velocity_year_6 (cm/year)	Female	2	5.00±4.243	4,80±3.90
	Male	3	4.67±4.619	
Height_velocity_year_7 (cm/year)	Female	1	5.00±0.00	7,00±2.83
	Male	1	9.00±0.00	
Height_velocity_year_8 (cm/year)	Female	1	0.00±0.00	3,00±4.24
	Male	1	6.00±0.00	
Mean height velocity (cm/year)	Female	4	6.72±1.07	8,29±1.98
	Male	9	8.99±1.91	
Total height gain (cm)	**Female**	**4**	**34.25±17.17**	**36,69±14.85**
	Male	**9**	**37.78±14.69**	

Table 4. Results of correlation analysis with Final Height Z-score as a dependent variable

Correlations		
		HAZ score at the end of treatment (Final HAZ score)
	Pearson Correlation	Sig. (2-tailed)
Age_at_starting_treatment	-.529	.031
HAZ_at_start_of_treatment	.758	.001
HAZ_change_by_puberty_start	.371	.001
Duration_of_treatment	.515	.036
HAZ_before_puberty	.51	.035
Bone_age_deficit	-.477	.050
Dose_of_GH	.104	.368
Mid_ Parental_HAZ_score	.273	.184



Graphic 2. The ratio between final height and MPH±6.5cm

With an impressive gain of 1.08±0.28 z-score within first year of treatment and total HAZ score change from starting treatment with 2.31±0.75 z-score, 69.2% of our patients achieved final height within the target height range. The mean pubertal height gain was 1.88±0.94 z-score which was compared to study by August *et al.* (2011) but higher to studies by **Westphal *et al.* (2008)**. However the lower final height SDS achieved compared to results from (**Westphal *et al.***, (16.60±1.79 years vs18 years) and shorter duration of treatment (4.54±2.14years 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 but it failed to produce consistent attainment of full genetic potential which may be due to suboptimal dosing and shorter duration of

treatment (**Guyda, 1999; Carel *et al.*, 2002; August *et al.*, 2011**). However many studies concluded that given optimal treatment, patients with idiopathic growth hormone deficiency may achieve their genetic potential (**Westphal and Lindberg, 2008; Reiter *et al.*, 2006; Thomas *et al.*, 2001; Cutfield *et al.*, 1999**). In regards to our results, it was 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 lower end of normal for majority of our patients and full genetic potential was not always achieved by all patients. Correlation analysis showed that only 6 variables were good correlated with the final HAZ outcome in our patients, i.e. age at the start of treatment, height z-score at start of treatment, HAZ score change by puberty, duration of treatment, HAZ score before onset of puberty and bone age deficit. Age of starting treatment was significantly positively correlated with the final height outcome in our patients, similar with **Ranke *et al.* (2005)** reported. Therefore, early diagnosis and initiation of treatment is determinant to the final height outcome. This will prevent severe height deficit at the start of treatment and allow opportunity for these children to make up much of their height deficit before puberty as the percentage of final height that is gained during puberty may be biologically limited (**August *et al.*, 2011**). Older age of starting treatment among our patients had caused a narrow window period for treatment. Therefore, those with severe height deficit at start of treatment and at the onset of puberty would be shorter as an adult.

Growth hormone dose was not related to the final height outcome. Similar finding had also been reported by **Carel *et al.* (2002)** However growth hormone dose is one of the crucial final height predictors in patients with idiopathic isolated growth hormone therapy (**Mauras *et al.*, 2000; Ranke *et al.*, 2003**). This study was limited by its small sample size, which was due to small number of treated patients who had attained final height. Nevertheless, 69.2% of patients reached the final height within the target of genetic height.

Conclusion

69.2% our patients with idiopathic isolated growth hormone deficiency treated with growth hormone able to achieve their genetic height potential. Despite starting treatment late, they managed to gain 2.31±0.75 HAZ score in height and the final height for majority of them 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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