

Final Height in Growth – Hormone – Treated Children with Idiopathic Growth Hormone Deficiency: The Malaysian Experience

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INTRODUCTION

Growth hormone has been used in the treatment of short stature since 1957¹. 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in 1985 made available a reliable, virtually unlimited resource² to replace human pituitary growth hormone (which was withdrawn due to reported cases of Creutzfeldt-Jakob disease).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 therapy³. 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 Malaysia, the use of growth hormone increased slowly since 1985 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 that affecting final height in our local population has not been available. This study aims to evaluate the final height outcome among the Malaysian children diagnosed with idiopathic growth hormone deficiency treated with recombinant human growth hormone.

MATERIALS AND METHODS

This was a retrospective cohort study. The medical records of all patients who were on growth hormone therapy in the Pediatric Endocrine Unit, Universiti Kebangsaan Malaysia Medical Centre were reviewed. Only patients with idiopathic growth hormone deficiency [isolated GHD or multiple pituitary hormone deficiencies (MPHD)] who had attained final height were included in this study. Patients with syndrome/tumors/other systemic diseases were excluded.

The diagnosis of idiopathic growth hormone deficiency was defined based on the fulfillment of both the auxological and biochemical criteria. For auxological criteria, patient was short (height less than 3rd centile), slowly growing with poor height velocity for age less than 7cm/year (for patients \leq 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 20 mU/L in two separate growth hormone stimulation tests.

Peripubertal children (girls $>$ 8 years old or boys $>$ 9 years old) were primed with sex steroid before the growth hormone stimulation test. Growth hormone level was measured by the chemiluminiscense method using the IMMULITE analyzer in our centre.

The following data were retrieved from patients' medical record: gender, diagnosis, mid parental height, chronological age, bone age and height at starting treatment, predicted adult height at the start of 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 National Center for Health Statistics (NCHS) growth curves⁶ and were standardized by calculating their height SDS (Z-score). Onset of puberty was defined by achievement of testicular volume of 4 mls or more in boys or breast stage 2 in girls⁷.

Bone age was calculated from reading the plain radiograph of left hand and wrist by using the TW3 RUS method by single observer (author) and Predicted Adult Height (PAH) of patients were calculated based on current age, height and RUS score⁸. Bone age deficit was defined as (chronological age) – (bone age).

Mid parental height (TH) was defined by using Tanner's method⁹. 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 \pm 8.5cm. Final height (FH) 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 15 years or bone age more than 14 years in girls¹⁰. Mid parental height, predicted adult height and final height were then standardized by calculating their height SDS (Z-score) using the NCHS growth charts.

Results were expressed as mean \pm standard deviation (SD). Data was analyzed using the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). 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.

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Table I: Background demographic data of patients with Idiopathic GHD treated with recombinant human GH in University Kebangsaan Malaysia Medical Centre

	Male	Female	Total
IGHD	6	2	8
MPHD	6	3	9
Total	12	5	17

IGHD :Isolated growth hormone deficiency
 MPH: Multiple pituitary hormone deficiencies

Table II: Clinical characteristics of patients with Idiopathic GHD treated with recombinant human GH in University Kebangsaan Malaysia Medical Centre

n = 17	Mean ± SD (range)
Age at starting treatment (yr)	9.2 ± 1.7 (5.8-12.4)
Bone age deficit (yr)	4.4 ± 1.3 (2.0-7.0)
Mid Parental Height SDS	-1.3 ± 0.9 (-2.5 - 0.7)
Height SDS at start of treatment	-4.1 ± 1.1 (-6.7 to -2.9)
Predicted Adult Height SDS at start of treatment	-2.9 ± 1.3 (-5.1 to -0.8)
Δ Height SDS after first year of treatment	+1.0 ± 0.3 (0.5 – 1.5)
Height SDS at onset of puberty	-2.3 ± 1.0 (-3.9 to -0.3)
Pubertal Height gain SDS*	+0.3 ± 0.6 (-0.9 – 1.4)
Final Height SDS	-2.0 ± 1.0 (-3.6 – 0.0)
Δ Height SDS from start**	+2.1 ± 0.9 (0.3 – 3.4)
(Final Height SDS)-(Mid Parental Height SDS)	-0.7 ± 0.6 (-1.7 – 0.3)
(Final Height SDS)-(Predicted Adult Height SDS)	+0.9 ± 1.2 (-1.1 – 3.1)
Duration of treatment (yr)	6.3 ± 1.9 (2.9 – 10.0)
GH dose (mg/kg/day)	0.027 ± 0.003 (0.022-0.03)

*Pubertal Height gain SDS = (Final Height SDS) – (Height SDS at onset of puberty)
 **Δ Height SDS from start = (Final Height SDS) – (Height SDS at start of treatment)

Table III: Results of univariate correlation analysis with Final Height SDS as a dependent variable

	r	p value
Mid Parental Height SDS	0.834	0.000
Height SDS at start of treatment	0.612	0.009
Height SDS at onset of puberty	0.806	0.000

r = Pearson Correlation Coefficient

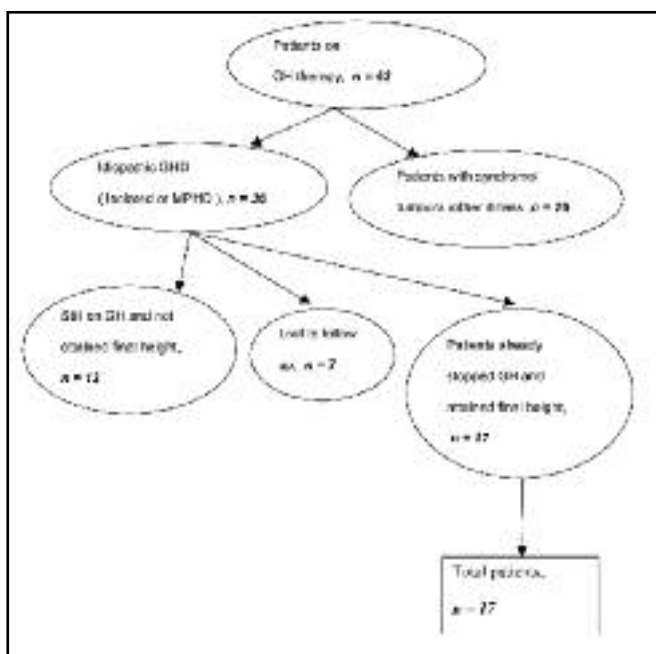


Fig. 1: Flow chart of study methodology.

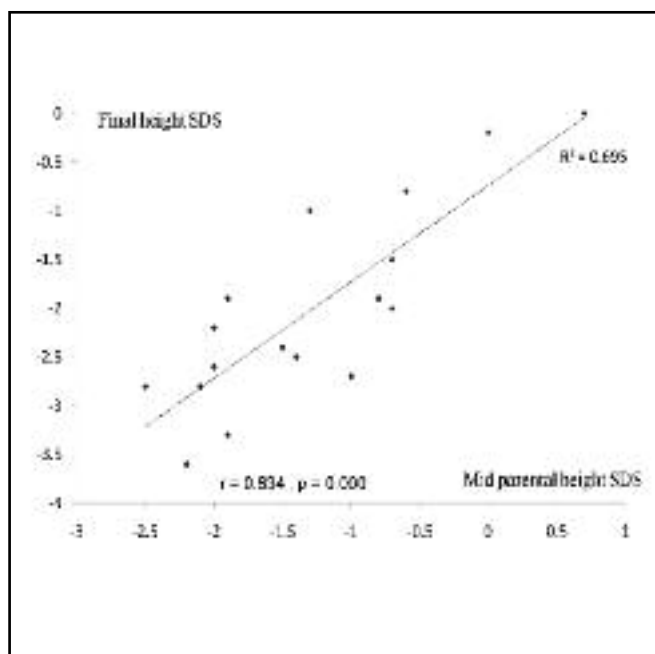


Fig. 2: Final height SDS in relation to mid parental height SDS.

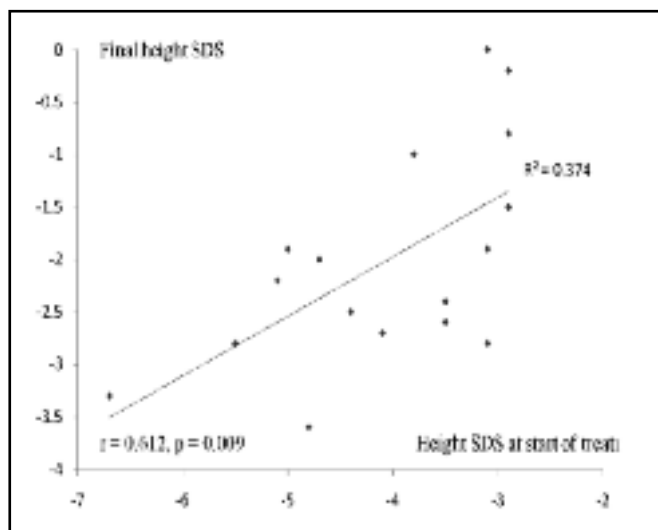


Fig. 3: Final height SDS in relation to height SDS at start of treatment.

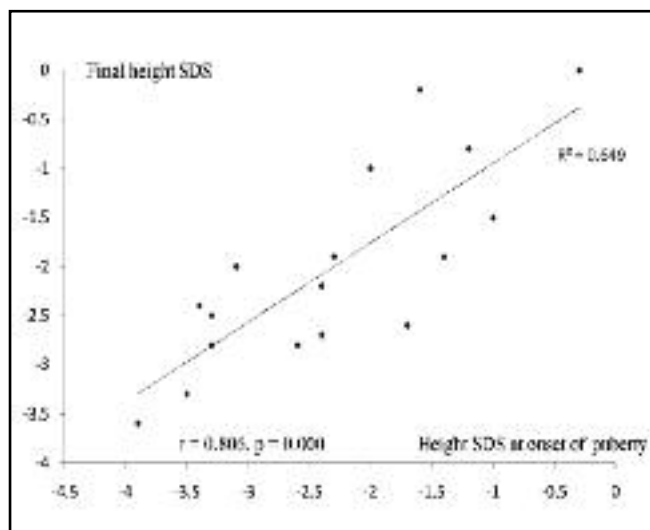


Fig. 4: Final height SDS in relation to height SDS at onset of puberty.

RESULTS

Among the 17 patients who were treated with growth hormone, the male : female ratio was 2.4 : 1.0 . 47% of them had isolated growth hormone deficiency while 53% had multiple pituitary hormone deficiencies.

The mean mid parental height SDS was -1.3 and the mean predicted adult height SDS based on bone age at starting treatment was - 2.9 SDS with the mean bone age deficit was 4.4 years . The mean age of starting GH treatment in our patients was 9.2 years old with boys started treatment later (9.7 years old) compared with girls (8 years old). This had resulted in severe height deficit of -4.1 SDS at start of treatment. After one year of treatment , almost all patients gained 1.0 SDS in height.

53% (9/17) of our patients had spontaneous puberty while the remaining 47% (8/17) were induced. The mean age of spontaneous puberty was 11.9 years while mean age of induced puberty was 13.1 years. Overall, the mean age of puberty was 12.5 years old with male attained puberty later (12.6 years old) compared with girls (12.1 years old). The mean height SDS at onset of puberty was -2.3 SDS and our patients gained average + 0.3 SDS during puberty. The Δ Height SDS from starting treatment was + 2.1 SDS with the mean final height SDS -2.0, achieved around the mean age of 16.5 years old. Among the cohort, there was one boy who entered spontaneous puberty at age of 9.7 years. In view of family circumstances and funding, the puberty was not suppressed and the final height SDS was -3.6 attained at 14.2 years old.

15 out of 17 patients (88%) achieved their genetic height potential where the final height corrected for mid parental height [(final height SDS) – (mid parental height SDS)] were within the target height range . However , majority of them still fall short of their mid parental height by -0.7 SDS.

On the other hand, final height corrected for predicted adult height based on bone age at start of treatment [(final height

SDS) –(predicted adult height SDS)] showed a positive gain of 0.94 SDS. This showed that growth hormone treatment had improved the final height outcome in treated patients compared to without treatment. The mean duration of growth hormone treatment was 6.3 years and the average GH dose was 0.027 mg/kg/day.

When we performed Pearson correlation analysis between final height SDS with various parameters listed in Table I, we found that only 3 variables were positively correlated with the final height outcome in our patients, i.e. mid parental height SDS, height SDS at start of treatment and height SDS at onset of puberty . Other variables such as age of starting treatment, change in height SDS after first year of treatment, duration of treatment and growth hormone dose were not statistically related to the final height outcome in our patients.

DISCUSSION

The above study reflected our early experiences in using recombinant human growth hormone in patients with idiopathic growth hormone deficiency. The mean age of starting treatment in our patients was 9.2 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 SDS -4.1. 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 -2.3. With an impressive gain of +1.0 SDS within first year of treatment and Δ Height SDS from starting treatment was +2.1 SDS , 88% of our patients achieved final height within the target height range. However, majority of them achieved final height at the lower target height range with -0.7 SDS from the mid parental height.

The mean pubertal height gain SDS was +0.31 which was actually lower compared to the National Cooperative Growth Study experience¹³ but comparable to studies by Westphal *et al*⁴. However the lower final height SDS achieved compared to results from Westphal *et al* might be explained by earlier age of attaining final height in our patients (16.5 years vs 18 years), shorter duration of treatment (6.3 years vs 8.5 years) and lower growth hormone dose (0.027mg/kg/day vs 0.033mg/kg/day) in our cohort .

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^{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, 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 3 variables were significantly related to the final height outcome in our patients i.e. mid parental height SDS, height SDS at start of treatment and height SDS at onset of puberty. Mid parental height SDS had the greatest influence on final height. This was obvious, as 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 start of treatment and at the onset of puberty would be shorter as an adult.

Even though age of starting treatment was not significantly correlated with the final height outcome in our patients, Ranke *et al*¹⁵ reported that in their patients who started treatment less than 3 years of age compared with those 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 detrimental 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 limited¹³. It is obvious now that the most successful strategies for enhancing growth hormone induced growth must concentrate on growth during early childhood⁵. However for adolescent 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 SDS without increasing the rate of skeletal maturation¹⁶.

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 However growth hormone dose is one of

the crucial final height predictors in patients with Turner Syndrome and patients born small for gestation age^{17,18}.

This study was limited by its small sample size, which was due to small number of treated patients who had attained final height. As a result, we were unable to perform multivariate regression analysis to determine factors that could have predicted the final height outcome in our patients.

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 +2.1 SDS in height and the final height for majority of them were 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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