Growth Pattern and Skeletal Maturation Following Growth Hormone Therapy in Growth Hormone Deficiency: Factors Influencing Outcome

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Objective: *To evaluate pattern of growth and skeletal maturation following growth hormone (GH) therapy in children with GH deficiency (GHD) with special emphasis on factors influencing outcome.* ***Methods:*** *Records of ninety-six children (67 boys, 29 girls) with GHD treated with GH for 2.3 ± 2.1 years were reviewed.* ***Results:*** *Height SDS at the end of treatment was significantly higher than that at initiation (–3.4 ± 1.7 versus –4.8 ± 1.6, P <0.001); it was however lower than target height SDS (corrected height SDS (1.8 ± 1.6, P <0.001). The greatest increase in height SDS was observed during the first two years of treatment. Kaplan Meier survival analysis showed that 92% of all subjects achieving end height SDS in the target height range did so within the first two years of treatment. Height SDS for bone age increased by 0.7 ± 0.9 during treatment (from –2.5 ± 1.0 to –1.8 ± 1.5, P < 0.001); the increase was however lower compared to that for height SDS for chronological age (P <0.01) suggesting inadvertent skeletal maturation. End height SDS was influenced by duration of treatment and corrected height SDS on multivariate analysis.* ***Conclusion:*** *GH treatment improves growth parameters in GHD; height however still remains compromised. Most of the catch-up growth occurs within two years of treatment emphasizing the need of optimal treatment during this period. Inadvertent skeletal maturation during treatment indicates a need for evaluating the role of agents effective in retarding skeletal maturation.*

Key words: *Growth hormone deficiency, Growth hormone therapy, Skeletal maturation*

TREATMENT with recombinant growth hormone (GH) has dramatically improved auxological outcome in growth hormone deficiency (GHD) with final height in the target height range(1-5). The response is however variable and a significant number of subjects fail to achieve their genetic potential(6). This is particularly true for developing countries where economic constraints limit the dose and duration of therapy. An understanding of factors influencing response is essential for improving outcome. There is a paucity of published data on factors influencing response to GH in developing countries. Inappropriate skeletal maturation has been suggested as a factor responsible for epiphyseal fusion and inadequate response to GH treatment in GHD(7). An understanding of pattern of skeletal maturation during GH therapy has become increasingly relevant with the advent of newer selective aromatase inhibitors. These drugs, inhibitors of estrogen production and skeletal maturation, have been used for improving height outcome in GHD with variable success(8). We evaluated growth pattern and skeletal maturation following GH therapy in children with GHD with special emphasis on factors influencing outcome.

Subjects and Methods

Children with GHD treated with recombinant GH for more than one year in the Pediatric Endocrine Clinic of our hospital were

included in the study. GHD was diagnosed in the presence of short stature (height SDS ≤ 2) and peak growth hormone levels less than 10 ng/mL following two standard provocative tests (clonidine and insulin tests).

GH was administered subcutaneously, daily at bedtime in a dose of 0.07-0.1 IU/kg/day. Subjects with multiple pituitary hormone deficiency were treated with appropriate hormone replacement to achieve normal hormone levels. The children were followed up three monthly for height, weight and pubertal status. Height was measured using stadiometer (Hultafors AB, Hultafors, Sweden) in triplicate and the average value was recorded. Bone age was estimated at initiation of treatment, six months later and yearly thereafter by the same radiologist (AKG) using the RUS score of Tanner Whitehouse 2 method (TW2 method)(9). Target height was calculated using the measured parental height according to standard formula [Target height = (Father's height + Mother's height) ÷ 2, + 6.5 cm for boys and –6.5 cm for girls]. Height was expressed as standard deviation score (SDS) for chronological and bone age according to the NCHS data using the standard formula [SDS = (Measured height – Mean height for age) ÷ standard deviation for age](10). Corrected height SDS was calculated by subtracting target height SDS from height SDS.

SPSS for windows version 10 was used for statistical analysis. Paired Student's *t* test was used for comparing initial and final values while unpaired *t* test was employed for independent parameters. Stepwise linear regression analysis was performed to evaluate factors influencing end height SDS and increase in height SDS. Factors found significant on univariate analyses were included in the multivariate model. Regression coefficients were calculated on multivariate analysis to assess the impact of individual factors on the dependent variable. Chi square test was used to compare the proportion of subjects in both the groups who achieved height in the target height range. Kaplan Meier survival analysis was performed to characterize the dynamics of catch up growth. *P* value less than 0.05 was considered significant. Values have been expressed as mean ± standard deviation unless specified.

Results

Ninety-six children (67 boys, 29 girls) with GHD were treated with GH at the Pediatric Endocrine Clinic of our hospital from 1990 to 2005. GHD was secondary to neuro-surgery in nine (9.4%, six with craniopharyngioma and three with arachnoid cyst); no cause was identified in the remaining eighty-seven subjects (91.6%). Seventy-nine subjects (82.3%) had isolated GHD; nineteen had concomitant anterior pituitary hormone deficiencies (17.7%). The peak GH levels were 3.7 ± 2.8 ng/mL. GH treatment (0.07 ± 0.02 IU/kg/day) was initiated at the age of 9.9 ± 3.7 years (range 2.8-17.6 years) and was continued for 2.3 ± 2.1 years (range 1-9.4 years) till the age of 12.2 ± 3.8 years. Seventeen subjects were pubertal at the initiation of GH therapy. Initial height SDS was significantly lower than the target height SDS (–4.8 ± 1.6 as against –1.6 ± 0.9, $P < 0.001$). Height SDS was in the target height range (corrected height SDS > – 2) in 17 subjects (17.7%).

Growth pattern and skeletal maturation

Treatment led to significant increase in growth velocity during the first year of treatment (from 1.9 ± 1.0 cm/year to 10.3 ± 2.9 cm/year range 4.5-18 cm/year, P <0.001) followed by decrease to 7 cm/year in the second year (*Fig. 1*). This was associated with

increase in height SDS by 1.7 during the first two years of treatment (*Fig. 2*). Growth velocity remained stable during the subsequent follow-up and resulted in increase in height SDS by 0.6 over the next three years (*Fig. 2*). Survival analysis demonstrated that 92% of all subjects (46 out of 50) who achieved end height SDS in the target height range (corrected height SDS > – 2) did so within two years of therapy (*Fig. 3*). Height SDS at the end of treatment was significantly higher compared to that at initiation (–3.4 ± 1.7 versus –4.8 ± 1.6, $P < 0.001$) but was lower than target height SDS (corrected height SDS –1.8 ± 1.6, $P < 0.001$, *Table I*). Greater proportion of subjects had height SDS in target height range at the end of treatment compared to that at initiation of therapy (52.1% as against 17.7%, $P < 0.001$). Bone age increased from 7.1 ± 3.3 years at initiation to 9.8 ± 3.7 years at discontinuation of GH treatment. Height SDS for bone age increased by 0.7 ± 0.9 during treatment (from –2.5 ± 1.0 to –1.8 ± 1.5, $P < 0.001$, *Table I*); the increase was however lower compared to that for height SDS for chronological age ($P < 0.01$, *Fig. 2*). Bone age to chronological ratio (BA : CA) increased by 0.1 ± 0.1 (from 0.7 ± 0.2 to 0.8 ± 0.2, $P < 0.001$).

Factors influencing outcome

Subjects with end height SDS in the target height range had higher initial BA : CA and were treated for longer duration compared to those with height SDS lower than the target height range (*Table II*). No influence of disease form (idiopathic or organic), pattern of pituitary involvement (IGHD or MPHD), age at treatment, peak GH levels and GH dose on end height SDS was observed (*Table III*). Duration of treatment, corrected height SDS and initial bone age to chronological age ratio correlated significantly with end height SDS on univariate analysis; the effect for duration of treatment and corrected SDS remained significant on multivariate analysis (*Table III*). Increase in height SDS correlated positively with duration of treatment, initial corrected SDS and first year growth velocity and

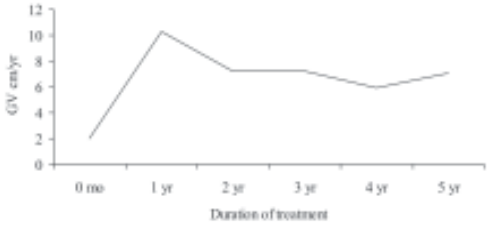

Fig.1. Line diagram demonstrating trend of growth velocity over time.

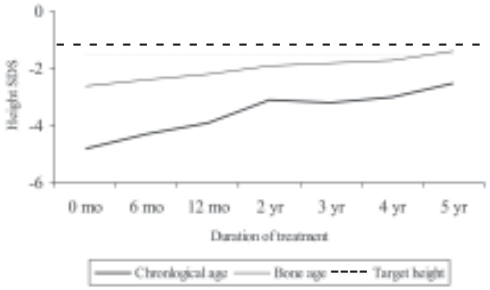

Fig.2. Line diagram demonstrating trend of height SDS for chronological age and bone age following therapy.

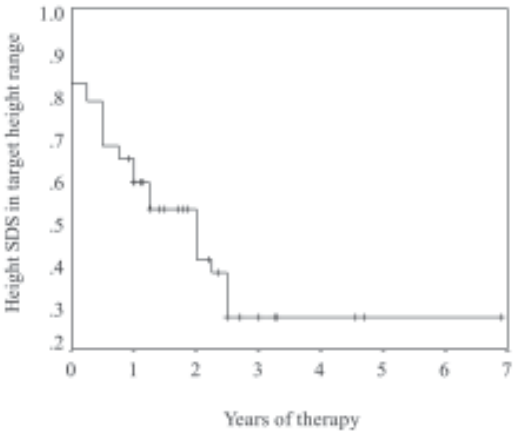

Fig.3. Kaplan Meier survival curve demonstrating proportion of subjects with height SDS in the target height range.

TABLE I–*Comparison of Parameters Following GH Treatment*

Parameter	Initial	Final	Increase	P*
Height SDS	–4.8 ± 1.6	–3.4 ± 1.7	1.4 ± 0.8	< 0.001
Height SDS for bone age	–2.5 ± 1.6	–1.8 ± 1.5	0.7 ± 0.9	< 0.001
Corrected height SDS	–3.2 ± 1.8	–1.8 ± 1.6	1.2 ± 0.8	< 0.001
Bone age/ chronological age	0.7 ± 0.2	0.8 ± 0.2	0.1 ± 0.1	< 0.001
Corrected height SDS ≥2	17(17.7%)	50 (52.1%)	33 (34.4%)	< 0.001

SDS = standard deviation score, expressed as mean ± standard deviation.
* Indicating significance of difference for parameters at initiation and discontinuation of GH treatment.

TABLE II– *Comparison of Individuals with End Height SDS in Target Height Range*

Parameter	Corrected end height SDS		p*
	> –2	<–2	
Age at treatment (yr)	9.6 ± 3.6	10.3 ± 3.8	NS
Duration (yr)	2.9 ± 2.5	1.6 ± 1.2	0.001
Peak GH (ng/mL)	3.6 ± 2.8	3.9 ± 2.8	NS
Bone age/ chronological age	0.8 ± 0.2	0.7 ± 0.2	0.02
Pituitary involvement			
Isolated	37	41	0.07
Multiple deficiency	12	5	

SDS = standard deviation score, NS = not significant, expressed as mean ± standard deviation.
* Indicating significance of difference for subjects with and without end height SDS in the target height range.

negatively with peak GH levels (*Table III*). The effect of treatment duration, initial corrected height SDS and first year growth velocity was maintained on multivariate analysis (*Table III*).

Discussion

Findings of our study suggest that GH therapy significantly improves auxological outcome in Indian children with GHD. End height SDS was significantly higher than that at initiation and was in the target height range in 52.1% subjects as against 17.7% at the initiation of treatment. The response is however worse compared to developed countries where height SDS similar to target height SDS has been reported(1-5). This may be related to delayed diagnosis with greater height compromise, lower GH dose, shorter duration of treatment, and compromised nutritional status. GH treatment was initiated significantly later in our subjects compared to the studies from the western countries(4,5). Age at initiation of GH treatment has been shown to be negatively correlated to response to therapy emphasizing the need of early diagnosis and treatment of the condition(3,4).

Lower GH dose and shorter duration of treatment in our subjects are linked to self-procuring of GH as against state or insurance funded treatment in most developing

TABLE III– *Factors Influencing Response to GH Therapy*

Univariate				
Parameter	Height SDS		Increase in height SDS	
	r	p	r	p
Age at treatment	–0.13	NS	–0.17	NS
Duration	0.20	0.004	0.42	<0.001
Corrected HSDS	0.55	<0.001	0.35	<0.001
BA/CA	0.31	0.002	–0.18	0.08
GH dose	–0.14	NS	–0.01	NS
Peak GH	–0.07	NS	–0.24	0.02
GV first year	–0.04	NS	0.46	<0.001
Multivariate				
	Height SDS		Increase in height SDS	
	Beta	p	Beta	p
Corrected HSDS	0.58	<0.001	–0.28	0.001
BA/CA	0.17	NS	–	–
Duration	0.27	0.02	0.44	<0.001
Peak GH	–	–	–0.12	NS
GV first year	–	–	0.44	<0.001
R^2	45%	48.1%		

HSDS = Height SDS; BA/CA = Bone age to chronological age ratio, GV = Growth velocity, NS = Not significant.

countries. The dose of GH in our study (0.07 ± 0.002 IU/kg/day) is definitely lower compared to currently employed dose in developed countries (the dose of GH employed in United States is around 0.14 IU/kg/day). Studies have demonstrated a dose-response relationship of GH in GHD with higher doses (up to 0.3 IU/kg/day) associated with better response (11,12). Normal weight for height and serum albumin levels precludes malnutrition as a major cause of poor response in our subjects. The effect of zinc deficiency, an established cause of growth retardation, can however not be excluded.

Maximum catch-up growth was achieved during the first two years of treatment. Survival analysis suggested that treatment for two years was associated with end height SDS in the target height range. This along with the observation that the first year growth response is an important predictor of increase in height SDS emphasizes the need for careful management during the first two years of therapy. This finding also has implications on the desirable duration of treatment in resource poor settings where treatment till final height is often not feasible. Our study suggests that to achieve optimal catch up growth GH should be

Key Messages

- Growth hormone therapy significantly improves height outcome in growth hormone deficiency.
- Duration of treatment and initial corrected height SDS are important determinants of response to therapy.
- Growth hormone treatment is associated with inadvertent skeletal maturation.

continued for a minimum period of two years. Treatment for shorter duration is not expected to result in significant increase in height and may therefore not be cost-effective.

Duration of treatment and initial corrected height SDS emerged as important predictors of end height SDS. Early diagnosis with less growth compromise and prolonging the duration of GH therapy is therefore expected to improve height outcome. This emphasizes the need for increasing the duration of therapy and diagnosis at an early stage with lower growth compromise for improving outcome. Higher end height SDS in individuals with higher initial height SDS has been reported in previous studies on GH therapy in GHD and indicates a trend for target height seeking(3,4). This is reiterated by the observation that individuals with greatest height compromise at initiation had greatest increase in height, a finding that has been observed in other reversible causes of growth retardation following correction of the underlying cause(13). Lack of effect of age at treatment on response may be related to preservation of bone age and therefore growth potential in majority of the subjects.

An important observation of our study was inappropriate skeletal maturation during GH therapy as reflected by an increase in bone age to chronological age ratio and lower increase in height SDS for bone age compared to that for chronological age. This phenomenon has been reported in children with hypothyroidism following thyroid replacement and has the risk of premature epiphyseal fusion and compromised height(14). This observation has led to the use of gonadotropin releasing hormone analog for improving height outcome in children with hypothyroidism(15). Development of highly selective aromatase inhibitors, inhibitors of estrogen synthesis and skeletal maturation, provides a window of opportunity for retarding inadvertent skeletal maturation induced by GH. Preliminary studies have failed to demonstrate increase in predicted height following addition of aromatase inhibitor anastrazole for one year; long-term follow-up is however awaited(8). There is a need of systematic evaluation of the effect of these agents on skeletal maturation and final height in GHD.

Contributors: AB, MK and PSNM were involved in management of patients. AKG reviewed the bone age of all the subjects. AB planned the study, collected data, performed the statistical analysis and drafted the manuscript. MK was involved in planning of the study and reviewed the script. PSNM was involved in planning the study, critically reviewed the manuscript and would act as the guarantor of the study.

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