Original Article

Long-term Response to Recombinant Human Growth Hormone Therapy in Indian Children with Growth Hormone Deficiency

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Abstract

Background: Growth hormone deficiency (GHD) remains the most common indication for use of recombinant human growth hormone (rhGH) therapy in clinical practice. However, there is a paucity of studies focusing on long-term response to rhGH therapy in the Indian context. **Aim:** To determine the response to rhGH therapy and its predictors in children with GHD followed up at a tertiary care center in North India. **Materials and Methods:** We performed a retrospective review of the records of children with GHD who received rhGH therapy for at least 1 year. The relevant anthropometric, biochemical and radiological data at baseline and follow-up were recorded**. Results:** A total of 99 children (64 boys, 35 girls; 61 isolated GHD, 38 multiple pituitary hormone deficiency) were studied. The mean (±SD) age and height SDS at treatment initiation were 12.4 (±3.0) years and −4.0 (±1.1) respectively, while median (IQR) serum insulin-like growth factor 1 (IGF-1) and peak growth hormone level on clonidine stimulation were 73 (25-167) ng/ml and 1.1 (0.4-3.6) ng/ml respectively. The height velocity was highest during the first year of treatment (10.6 ± 3.0 cm/year), declining to 8.7 ± 2.7 and 7.9 ± 2.2 cm/year during second and third year, respectively. Over the subsequent years, there was further graded fall in height velocity, declining to 4.8 ± 3.6 cm/year (n = 2) during the seventh year. The height gain during first year was negatively correlated with age at initiation of treatment, baseline height SDS, baseline serum IGF-1 and peak serum GH level on GH stimulation test, while it showed a positive correlation with bone age delay at baseline. Only baseline height SDS was found to have a significant negative correlation with height gain during the second year. **Conclusions:** This study provides data on long-term response to rhGH therapy and its predictors in Indian children with GHD.

Keywords: Growth hormone deficiency, height velocity, India, predictors of response, recombinant human growth hormone

Introduction

The term short stature is used for a child whose height is two standard deviations (SD) or more below the mean for children of that age and gender. Short stature affects approximately 2%-3% children in a given population.[1,2] Its most common causes are constitutional delay of growth and development (CDGD) and familial short stature (FSS), both considered as variants of normal growth. Growth hormone deficiency (GHD) is a relatively less common, but an important cause of short stature, diagnosed on the basis of careful clinical and auxological assessment, combined with biochemical and radiological evaluation.[3,4]

Recombinant human growth hormone (rhGH) treatment has been shown to improve auxological outcomes in children with GHD.[5,6] However, delays in diagnosis and treatment initiation, and financial constraints leading to inadequate dosing, premature treatment discontinuation and frequent interruptions are some of the unique challenges with the use of rhGH therapy in the Indian context.[7] Further, there is a paucity of studies that report the long-term response to rhGH therapy in Indian children with GHD.

With this background, the present study was done to determine the long-term response to rhGH therapy and its predictors in 99 children with GHD being followed up in the pediatric and

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adolescent endocrinology clinic at a tertiary care center in North India.

Materials and Methods

Settings and study design

A retrospective record review of children referred to the pediatric and adolescent clinic (Department of Endocrinology and Metabolism, AIIMS, New Delhi) for evaluation of short stature (between January 2000 and December 2017) was done. Subjects diagnosed to have GHD, and treated with rhGH for at least 1 year were included in the analysis. Any subject who discontinued the therapy for more than 2 weeks was excluded. Because this was a retrospective study, with no intervention involved, and as strict patient confidentiality was maintained, ethical clearance was not sought.

Anthropometric and pubertal evaluation

All measurements were made by skilled staff with participants dressed in minimal light clothing and without footwear. Height was measured to the nearest 0.1 cm using portable Holtain's stadiometer (Holtain Inc., Crymych, Pembs. UK) with the child standing straight, and head held in Frankfurt horizontal plane. Weight was measured to the nearest 0.1 kg using an electronic scale. The measurements were taken twice, and the mean was recorded as final. The scale and stadiometer were calibrated using standard weight and height respectively. The uniformity of staff was maintained for all measurements. Mid-parental height (MPH) was computed based on height provided by the parents (father's height + mother's height) / 2, + 6.5 cm for boys and −6.5 cm for girls). All anthropometric measurements were plotted on KN Agarwal growth charts. Height was expressed as standard deviation score (SDS) according to the formula: Height SDS = (Measured height − Mean height for age)/SD for age.

In boys, testicular volume (TV) was assessed by comparative palpation with Prader orchidometer to the nearest milliliter. A TV of ≥4 ml in boys and presence of thelarche in girls was considered as evidence of onset of puberty.

Diagnosis of GHD

GHD was suspected in children with short stature (height <−2 SDS) who had normal initial investigative work-up for other causes. GH stimulation test (GHST) was performed using clonidine and glucagon (where necessary) in a sequential manner. A peak serum GH level >10 ng/ml at any time point during a GHST was considered as normal, excluding GHD. According to the departmental protocol, a peak serum GH level <5 ng/ml during the first stimulation test (clonidine) was considered as an adequate evidence for the diagnosis of GHD, and a second stimulation test (glucagon) was skipped in such cases. However, in cases with peak serum GH level between 5 and 10 ng/ml, a second stimulation test (glucagon) was carried out to confirm the diagnosis. A peak serum GH level <10 ng/ml was considered as diagnostic for GHD.

Radiological evaluation

All subjects with biochemical diagnosis of GHD underwent neuroimaging in the form of magnetic resonance imaging (MRI) of sellar and suprasellar region, except one where computed tomography was done. All subjects without any evident mass lesion were subsequently started on rhGH therapy. Subjects detected to have a mass lesion in the brain were referred for neurosurgical intervention, and rhGH therapy initiated after surgery, only when a documented evidence of no residual disease or stable residual disease (for 1 year) was available. Radiograph of the left hand and wrist was performed at baseline and at yearly interval for bone age estimation (Greulich and Pyle method).

Assessment of other pituitary axis

All subjects underwent evaluation for other pituitary axis using appropriate hormone assays (serum T4, TSH, 8:00 am serum cortisol, plasma ACTH). The diagnostic testing for GHD in subjects with preexisting central hypothyroidism and central hypoadrenalism was delayed till the time euthyroidism and eucortisolism was achieved. Evaluation of gonadtroph axis (serum LH, FSH, testosterone, estradiol and GnRH analogue stimulation test, where necessary) was performed in subjects who failed to enter puberty by the age of 13 years (girls) and 14 years (boys). Documentation of 24-hour urine output followed by serum and urine osmolality measurements were performed to evaluate posterior pituitary function, where required. Subjects with involvement of other pituitary axis were defined as having multiple pituitary hormone deficiency (MPHD), while those without any such involvement were defined as having isolated growth hormone deficiency (IGHD).

Hormone assays

Serum TSH, LH, FSH, prolactin and plasma ACTH estimation was done by electrochemiluminescent tracer-based immunometric assay (sandwich assay), while serum T4, cortisol, testosterone and estradiol were estimated by electrochemiluminescent tracer-based competitive immunoassay using Cobas e-411 auto-analyser (Roche Diagnostics, Mannheim, Germany). Serum GH and IGF-1 estimation was done by chemiluminescent tracer-based immunometric assay (sandwich assay) using Diasorin Liaison auto-analyser (Diasorin Inc., Stillwater, MN, USA). The internationally recommended recombinant 22 kDa GH standard (WHO 98/574) was adopted for the serum GH assay.[8]

GH replacement

rhGH was initiated at a dose of 0.20-0.30 mg/kg/week. Subjects were followed at 3-6 months interval for assessment of anthropometric and pubertal parameters, and for monitoring of adverse effects and development of central hypothyroidism. The dose of rhGH was adjusted on the basis of current weight and height velocity response; serum IGF-1 was used as an additional parameter from 2014 onwards.

Type of GH preparation used

The commonly available commercial preparations of rhGH were used, either in the form of syringe and vial or pre-filled

pen device. The innovator molecule (Norditropin, Novo Nordisk; Genotropin, Pfizer Pharmaceuticals) was used in 40 (40.4%) subjects, while biosimilar GH (Headon, Sun Pharmaceuticals) was used in remaining 59 (59.6%) subjects. Due to the lower cost of treatment, biosimilar GH was preferred, especially in patients receiving financial aid from government and non-government sources (in order to sustain treatment for a longer duration). Of the 40 subjects initiated on innovator molecule, 12 (30%) shifted to biosimilar GH after 6-12 months of therapy.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows (SPSS 21.0, SPSS Inc., Chicago, IL, USA). Data were presented as number (%), mean (±SD) or median (IQR) as appropriate. Quantitative variables that followed normal distribution were compared using Student's t-test for independent samples. Quantitative variables that did not follow normal distribution were compared using Wilcoxon rank-sum test. Pearson's correlation test (for normally distributed data) and Spearman's correlation test (for data not normally distributed) were used to determine the factors predicting height velocity response at year 1 and year 2. A *P* value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 99 subjects (64 boys, 35 girls) were included in the final analysis. In all, 73 subjects (73.7%) were pre-pubertal, while 26 (26.3%) were peri-pubertal at the time of treatment initiation. A total of 61 (61.6%) subjects had IGHD (40 boys, 21 girls), while other 38 (38.4%) had GHD as a part of MPHD (23 boys, 15 girls). In the MPHD group, 15 (39.5%) subjects had involvement of two pituitary axis, while 14 (36.8%) and 9 (23.7%) subjects had involvement of three and four pituitary axis respectively. The pituitary abnormalities seen (apart from GHD) were central hypothyroidism (n = 33; 33.3%), central hypoadrenalism (n = 21; 21.2%) and hypogonadotropic hypogonadism (n = 16; 16.2%). No subject was found to have posterior pituitary involvement in the form of diabetes insipidus (DI). Primary GHD was present in 94 (94.9%) subjects, while GHD was secondary to intracranial mass lesion (compressive and/or postoperative hypopituitarism) in 5 (6.8%) subjects.

The mean chronological age at treatment initiation was 12.4 ± 3.0 years (12.1 ± 3.1 years in IGHD group and 13.4 ± 2.8 years in MPHD group). The mean height and height SDS at baseline were 119.6 ± 16.3 cm (boys, 119.4 ± 17.7 cm; girls, 119.8 ± 13.6 cm) and −4.0 ± 1.1 respectively. The mean bone age and chronological age-bone age difference were 8.3 ± 3.1 years and 4.1 ± 2.0 years respectively [Table 1]. The median (IQR) serum insulin like growth factor-1 (IGF-1) and peak growth hormone level on clonidine stimulation were 73 (25-167) and 1.1 (0.4-3.6) ng/ml respectively.

Pre-pubertal subjects were more severely affected compared to peri-pubertal subjects (mean height SDS: −4.2 ± 1.4 vs −3.4 ± 1.4; $P < 0.05$). The mean chronological age-bone age difference (4.5 ± 1.8 years vs 3.1 ± 2.3 years; $P < 0.05$) was also significantly higher in pre-pubertal compared to peri-pubertal subjects [Table 2].

Response to GH therapy

All subjects completed 1 year of rhGH replacement, while 61, 38, 28 and 10 completed 2, 3, 4 and 5 years of rhGH replacement respectively. Fewer number of subjects completed 6 (n = 3) and 7 years (n = 2) of rhGH replacement.

The height velocity response was maximum during the first year of treatment (10.6 ± 3.0 cm/year), declining to 8.7 ± 2.7 and 7.9 ± 2.2 cm/year during the second and third years respectively. Over the subsequent years, there was further graded fall in height velocity response, declining to 4.8 ± 3.6 cm/year (n = 2) during the seventh year. The mean height SDS improved from −4.0 ± 1.1 at baseline to -3.1 ± 1.3 and -2.5 ± 1.0 at the end of year 1 and year 2 respectively. Over the subsequent years, height SDS improved further, reaching -1.9 ± 0.8 by the end of year 4 and −1.6 ± 0.6 by the end of year 5. Similarly, the mean difference of chronological age with bone age (bone age delay) showed a graded decrease over the period of follow-up [Table 1]. The height velocity response was not significantly different between the pre-pubertal and peri-pubertal groups [Table 2].

Comparison between IGHD and MPHD groups

At baseline, the mean age (13.4 ± 2.8 years vs 12.1 ± 3.1 years; $P < 0.05$) and chronological age-bone age difference (5.1 ± 1.9 years vs 3.6 ± 1.8 years; $P = 0.001$) was significantly higher in MPHD compared to the IGHD group. However, the

Table 1: Baseline characteristics and effects of rhGH replacement in subjects with GHD

Parameter	Baseline (n-99)	Year 1 (n-99)	Year 2 (n-61)	Year 3 (n-38)	Year 4 (n-28)	Year 5 (n-10)	Year 6 (n-3)	Year 7 (n-2)
Age (years)	12.4±3.0	13.4±3.0	14.1±2.8	14.1±2.6	14.8±2.4	15.1±2.7	13.4±1.3	14.2±1.7
Height SDS	-4.0±1.1	-3.1±1.3	-2.5±1.0	-2.1±0.9	-1.9±0.8	-1.6±0.6	-1.7±0.0.1	-1.6±0.03
Change in height SDS	N/A	0.9±0.4	0.7±0.4	0.5±0.4	0.4±0.4	0.4±0.3	0.3±0.1	0.2±0.1
Height velocity (cm/year)	N/A	10.6±3.0	8.7±2.7	7.9±2.2	7.1±2.3	6.8±2.3	6.5±2.5	4.8±3.6
Bone age delay (CA-BA) (years)	4.1±2	3.4±2.1	3.2±1.8	2.5±1.8	2.3±2.0	2.8±1.7	1.6±0.8	1.2±1.0
Serum IGF-1 (ng/ml)[#]	73 (25-167)	221 (152-365)	281 (220-349)	340 (247-584)	444 (309-595)	NR	NR	NR

Data expressed as mean±SD and median (IQR)[#]. NR: Not reported due to small number of observations. BA: Bone age; CA: Chronological age; GHD: Growth hormone deficiency; IGF-1: Insulin-like growth factor 1; N/A: Not applicable; rhGH: Recombinant human growth hormone; SDS: Standard deviation score

two groups did not differ in terms of baseline height deficit (mean height SDS: −4.2 ± 1.5 vs − 3.9 ± 1.4; $P = 0.33$). There was no significant difference in height velocity response between the subjects belonging to the two groups during the first 4 years of rhGH replacement. The chronological age-bone age difference between the two groups remained significant after the first, but not second year of rhGH replacement [Supplementary Table].

Table 2: Comparison of baseline characteristics and effects of rhGH replacement in pre-pubertal and peri-pubertal subjects

Parameter	Pre-pubertal	Peri-pubertal	*P*
Baseline	*n*=73	*n*=26	
Age (years)	11.5±2.8	14.9±1.6	<0.001
Height SDS	-4.2±1.4	-3.4±1.4	0.01
Bone age (years)	7.1±2.5	11.8±1.6	<0.001
Bone age delay (CA-BA) (years)	4.5±1.8	3.1±2.3	0.003
Serum IGF-1 (ng/ml)#	47.1 (25.0-141.2)	162 (96-202)	0.097
Year 1	*n*=58	*n*=41	
Age (years)	11.9±2.7	15.5±1.7	<0.001
Height SDS	-3.2±1.4	-2.8±1.2	NS
Change in height SDS	0.98±0.42	0.84±0.45	NS
Height velocity (cm/year)	11.0±2.0	10.1±3.4	NS
Year 2	*n*=25	*n*=36	
Age (years)	12.8±2.7	15.0±2.6	0.002
Height SDS	-2.7±0.8	-2.3±1.1	NS
Change in height SDS	0.66±0.6	0.64±0.3	NS
Height velocity (cm/year)	8.85±2.7	8.7±2.7	NS
Year 3	*n*=16	*n*=22	
Age (years)	13.4±3.0	14.5±2.1	NS
Height SDS	-2.3±0.9	-2.1±0.9	NS
Change in height SDS	0.41±0.3	0.51±0.4	NS
Height velocity (cm/year)	7.3±2.0	8.3±2.3	NS
Year 4	*n*=8	*n*=20	
Age (years)	13.4±2.8	15.4±2.1	0.05
Height SDS	-1.96±0.8	-1.96±0.9	NS
Change in height SDS	0.23±0.2	0.5±0.4	NS
Height velocity (cm/year)	6.1±1.3	7.5±2.6	NS

Data presented as mean±SD and median (IQR)#, BA: Bone age; CA: Chronological age; IGF-1: Insulin-like growth factor 1; NS: Not significant; rhGH: Recombinant human growth hormone; SDS: Standard deviation score

Response with type of GH preparation used

There was no statistically significant difference in the height velocity response between subjects treated with innovator and biosimilar GH or pre-filled pen device and syringe/vial at any time point (data not presented).

Correlation of first and second year height velocity with various baseline parameters

A significant negative correlation was seen between first year change in height SDS and age at initiation of treatment, baseline height SDS, baseline serum IGF-1 and peak serum GH level while a significant positive correlation was seen with bone age delay (years). However, no significant correlation was observed between second year change in height SDS and any of the above parameters, except baseline height SDS for which a significant negative correlation was seen [Table 3].

Discussion

We have presented the long-term response to rhGH therapy in children with GHD from a tertiary care center in North India. The results from our study show that rhGH treatment results in a significant improvement in auxological outcome in the affected children. The mean height SDS improved from −4.0 SDS at baseline to >−2.0 SDS (normal stature for age- and gender-matched population) by the end of fourth year of treatment. The height velocity response was maximum during the first 3 years after treatment initiation, followed by a graded decline over the subsequent years. The factors which predicted height gain during the first year were chronological age, height SDS, serum IGF-1, peak serum GH level during GH stimulation test and bone age delay.

The mean baseline height deficit (−4.0 SDS vs −2.6 to −3.8 SDS) and bone age deficit (4.1 years vs 2.3-2.5 years) was much higher in our study compared to that reported from developed countries.[9,10] This could be attributed to the delayed presentation, lack of awareness regarding GHD, and the long lag period between diagnosis and treatment initiation (related to financial aspect of rhGH therapy) in our context. While the healthcare cost is borne by the state or health insurance in developed countries, the same is not true for developing countries like ours, where it is chiefly driven

Table 3: Correlation of treatment response during the first 2 years with various baseline parameters

Parameter	Height SDS change in 1st year	*P*	Height SDS change in 2nd year	*P*
Age at rhGH initation	-0.318	<0.001	0.089	0.496
Height SDS at baseline	-0.458	<0.001	-0.609	<0.001
Serum IGF-1 at baseline*	-0.277	0.05	-0.199	0.275
Peak serum GH on clonidine stimulation test*	-0.264	0.008	-0.209	0.106
Midparental height	0.048	0.663	0.098	0.482
Bone age at baseline	-0.427	<0.001	0.20	0.878
Bone age delay (CA-BA difference)	0.208	0.05	0.108	0.408

*Spearman's correlation test was used for these variables; Pearson's correlation test was used for remaining variables. BA: Bone age; CA: Chronological age; GH: Growth hormone; IGF-1: Insulin-like growth factor 1; rhGH: Recombinant human growth hormone; SDS: Standard deviation score

by patient's own pocket.[11] Treatment with rhGH has huge financial implications for the family, whose average monthly income could well be lower than average monthly cost of treatment. This would mean that a large number of children remain without treatment and suffer from severe height deficit. For the same reason, the data on response to rhGH therapy in Indian children with GHD is scarce. In our cohort, majority of families received financial help either from their employers or various health expenditure support schemes of the government of India. The cost of treatment was also sponsored by individual donations in some children.

The response to rhGH therapy in the Indian context has been studied previously; however, these studies have been limited by small sample size, short follow-up duration and inclusion of heterogenous patient population.[12-16] A comparison of results of these studies with our study has been provided in Table 4. The cut-off for diagnosis of GHD has been variable across these studies. While a peak GH <5 ng/ml on a single stimulation test was used by Kannan *et al*.,[12] others used a peak GH <7 ng/ml (Khadilkar *et al*.[14]) or <10 ng/ml (Menon *et al*.,[13] Bajpai *et al*.,[15] Garg *et al*.[16]) on two stimulation tests to diagnose GHD. This would imply that the severity of GHD was not uniform across studies; also, the baseline height SDS varied from −2.5 SDS (Menon *et al*.[13]) to −5.1 SDS (Khadilkar *et al*.[14]). The first year height velocity response in our study (10.6 ± 3.0 cm/year) was comparable to that seen in the studies by Kannan *et al*.,[12] Bajpai *et al*.[15] and Garg *et al*.[16] However, the response was lower compared to that reported by Khadilkar *et al*.[14] (12.1 ± 2.8 cm/year) and higher than one reported by Menon *et al*.[13] (8.0 ± 2.2 cm/year). It is known that the first year height response to rhGH therapy is inversely correlated to the severity of GHD, that is, children with higher severity of GHD and lower baseline height SDS are the ones likely to show maximum response to rhGH therapy. The subjects in study by Khadilkar *et al*.[14] had severe GHD with higher baseline height deficit, while those in the study by Menon *et al*.[13] were less severely affected, which could possibly explain the differences seen with our study.

The response to rhGH therapy was maximum during the first 3 years of treatment, and gradually declined over the subsequent years, a result consistent with other studies evaluating the long-term efficacy of rhGH therapy (Kannan *et al*.,[12] Bajpai *et al*.[15] and Garg *et al*.[16]). The height gain during first year showed a significant negative correlation with age, baseline height SDS, peak GH value, serum IGF-1 at baseline, and a significantly positive correlation with bone age delay at the baseline. In clinical practice, these could serve as important predictors of first year response to rhGH therapy, a parameter shown to have a strong positive correlation with total treatment-related height gain.[5,6] A negative correlation of age with first year height response emphasizes the importance of early diagnosis and treatment of childhood GHD.

Our study has several limitations. The study was retrospective in nature, and therefore may suffer from inadequacies inherent to such a study design. A follow-up data of >5 years was available only in very small number of participants ($n = 5$). This could be attributed to the delayed age at diagnosis and treatment initiation (mean age was 12.4 years), leading to treatment eligibility for a relatively short duration. Moreover, treatment discontinuation due to financial constraints after initial few years of therapy (in subjects who would otherwise require further treatment continuation) could also be contributory to this observation. Additionally, dose uptitration to the recommended weight based dose (0.3 mg/kg/week) could not be done in many subjects due to financial issues. We did not use higher dose of rhGH during pubertal years in any of the study participants. This strategy has been shown to be safe and efficacious in improving height outcomes in few studies,[17,18] but was not considered due to the significant additional cost involved. Lastly, the final height of the participants has not been reported in this study. The strengths of our study are its large sample size, homogenous study population, long follow-up duration, and reporting of the predictors of response to rhGH therapy.

To conclude, this study provides the data on long-term response to rhGH therapy and its predictors during the first 2 years in

Table 4: Comparison of various Indian studies on auxological outcomes of rhGH therapy

Author, Year	Study population	Sample size (*n*)	Age at treatment initiation	Baseline height SDS	Follow-up	First year height velocity
Kannan *et al*., 1991[12]	GHD	30 (M: 22, F: 8)	2-14 year	-3.8±1.1	Up to 5 years	10.9±2.2 cm/year
Menon *et al*., 1991[13]	GHD	20 (M: 10, F: 10)	9.4±3.7 year	-2.5±1.3	1 year	8.0±2.2 cm/year
Bajpai *et al*., 2006[15]	GHD (Mean stimulated GH=3.7 ng/ml)	96 (M: 67, F: 29)	9.9±3.7 year	-4.8±1.6	2.3±2.1 (1-9.4) years	10.3±2.9 cm/year
Khadilkar *et al*., 2007[14]	GHD (Mean stimulated GH=0.7 ng/ml)	15 (M: 11, F: 4)	12.0±2.8 year	-5.1±0.78	1 year	12.1±2.8 cm/year
Garg *et al*., 2010[16]	GHD, CKD, TS, PWS	71 (M: 46, F: 25)	10.0±3.2 year	Ht SDS: N/A Ht: 115.7±17.5 cm HA: 6.9±2.8 year	Up to 3 years	8.7±2.7 cm/year 9.8±2.9 cm/year in GHD group
Our study, 2019	GHD (Median stimulated GH=1.1 ng/ml)	99 (M: 64, F: 35)	12.4±3.0 year	-4.0±1.1	Up to 7 years	10.6±3.0 cm/year

CKD: Chronic kidney disease; F: Female; GHD: Growth hormone deficiency; HA: Height age; M: Male; N/A: Not available; PWS: Prader-Willi syndrome; SDS: Standard deviation score; TS: Turner syndrome

Indian children with GHD. Prospective studies with longer follow-up duration which report final height outcomes are needed in the near future.

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Conflicts of interest

There are no conflicts of interest.

References

1. Velayutham K, Selvan SSA, Jeyabalaji RV, Balaji S. Prevalence and etiological profile of short stature among school children in a South Indian population. Indian J Endocrinol Metab 2017;21:820-2.
2. Bramswig JH. Short and tall stature. Ann Nestle Eng 2007;65:117-27.
3. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: Summary statement of the GH Research Society. GH Res Society. J Clin Endocrinol Metab 2000;85:3990-3.
4. Goyal A, Khadgawat R. Diagnosis of childhood growth hormone deficiency: Controversies, consensus and need for new diagnostic tools. Neurol India 2018;66:1685-6.
5. Blethen SL, Baptista J, Kuntze J, Foley T, LaFranchi S, Johanson A. Adult height in growth hormone (GH)-deficient children treated with biosynthetic GH. The Genentech Growth Study Group. J Clin Endocrinol Metab 1997;82:418-20.
6. Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: Analysis of a large international database. J Clin Endocrinol Metab 2006;91:2047-54.
7. John M, Koledova E, Kumar KM, Chaudhari H. Challenges in the diagnosis and management of growth hormone deficiency in India. Int J Endocrinol 2016;2016:2967578.
8. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem 2011;57:555-9.
9. August GP, Julius JR, Blethen SL. Adult height in children with growth hormone deficiency who are treated with biosynthetic growth hormone: The National Cooperative growth study experience. Pediatrics 1998;102:512-6.
10. Darendeliler F, Lindberg A, Wilton P. Response to growth hormone treatment in isolated growth hormone deficiency versus multiple pituitary hormone deficiency. Horm Res Paediatr 2011;76:42-6.
11. Ahlin T, Nichter M, Pillai G. Health insurance in India: What do we know and why is ethnographic research needed. Anthropol Med 2016;23:102-24.
12. Kannan V, Usharani K. Human growth hormone therapy: Long term responses in 30 children with growth hormone deficiency. Indian J Pediatr 1991;58(Suppl 5):65-9.
13. Menon PSN, Virmani A, Sethi AK. Biosynthetic growth hormone therapy in children with growth hormone deficiency: Experience at AIIMS, New Delhi. Indian J Pediatr 1991;58(Suppl 1):71-7.
14. Khadilkar VV, Khadilkar AV, Nandy M, Maskati GB. Multicentric study of efficacy and safety of growth hormone use in growth hormone deficient children in India. Indian J Pediatr 2007;74:51-4.
15. Bajpai A, Kabra M, Gupta AK, Menon PSN. Growth pattern and skeletal maturation following growth hormone therapy in growth hormone deficiency: Factors influencing outcome. Indian Pediatr 2006;43:593-9.
16. Garg MK, Pakhetra R, Dutta MK, Gundgurthi A. Response to growth hormone therapy in Indian patients. Indian J Pediatr 2010;77:639-42.
17. Mauras N, Attie KM, Reiter EO, Saenger P, Baptista J. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: A randomized, multicenter trial. Genentech, Inc., Cooperative study groups. J Clin Endocrinol Metab 2000;85:3653-60.
18. Saenger P. Dose effects of growth hormone during puberty. Horm Res 2003;60:52-7.

Supplementary Table: Comparison of baseline characteristics and effects of rhGH replacement in subjects with IGHD and MPHD

Parameter	IGHD	MPHD	*P*
Baseline	*n*=61	*n*=38	
Age (years)	12.1±3.1	13.4±2.8	0.048
Height SDS	-3.9±1.4	-4.2±1.5	0.33
Bone age (years)	8.4±3.4	8.1±2.5	0.621
Bone age delay (CA-BA) (years)	3.6±1.8	5.1±1.9	0.001
Year 1	*n*=61	*n*=38	
Age (years)	13.0±3.0	14.3±2.8	0.053
Height SDS	-2.9±1.3	-3.4±1.3	0.157
Height velocity (cm/year)	10.9±3.2	10.1±2.4	0.224
Change in height SDS	0.95±0.5	0.85±0.4	0.313
Bone age delay (CA-BA) (years)	2.96±2.0	4.40±2.0	0.002
Year 2	*n*=40	*n*=21	
Age (years)	13.9±2.8	14.5±2.9	0.377
Height SDS	-2.4±1.0	-2.5±1.0	0.774
Height velocity (cm/year)	8.7±2.7	8.8±2.8	0.829
Change in height SDS	0.61±0.4	0.74±0.6	0.297
Bone age delay (CA-BA) (years)	2.9±1.9	3.8±1.6	0.069

Data presented as mean±SD. BA: Bone age; CA: Chronological age; IGHD: Isolated growth hormone deficiency; MPHD: Multiple pituitary hormone deficiency; rhGH: Recombinant human growth hormone; SDS: Standard deviation score