DOI: 10.7860/JCDR/2023/60560.17417

Original Article

Paediatrics Section

# Effect of Growth Hormone Therapy in Indian Children with Short Stature- A Retrospective Study

RUCHI MISHRA[1], SMRITI ROHATGI[2], JYOTI BAGLA[3], RAJEEV KUMAR MALHOTRA[4]




## ABSTRACT

**Introduction:** The causes for short stature are multifactorial. The recombinant Growth Hormone (rGH) is used worldwide for its treatment, however, there is paucity of data on use of growth hormone in Indian Children.

**Aim:** To study the effect of rGH in Indian children with short stature, who were enrolled under ESIC scheme.

**Materials and Methods:** This was a retrospective observational study. Subjects, who had short stature and diagnosed to have Growth Hormone Deficiency (GHD) by stimulation test and other causes for which growth hormone was indicated were enrolled. All subjects received treatment at ESI PGIMSR Basaidarapur, New Delhi, India, from July 2016 to July 2020, without discontinuation for more than one week. The data regarding gain in height was collected at the end of first year and then, at the end of second year. Height velocity and change in Height SD were calculated (Mean±Standard Deviation). The associations and correlations were calculated by Spearman's correlation test.

**Results:** The present study included data of 27 children (19 males and eight females) with short stature. The mean age at treatment initiation was 9.85 years±3.04. The most common aetiology for which growth hormone was started was Idiopathic GHD (IGHD) seen in (15/27) 55.5% followed by Multiple Pituitary Hormone Deficiency (MPHD) 18.5% (5/27). The mean height and height SD at baseline was 111.76 cm±17.40 and -3.85±1.19 (-6.0 to -1.5), respectively. The mean bone age delay (chronological age-bone age difference) was 40.96±25.58 months. The height velocity response was maximum during the first year of treatment (8.74±2.59 cm), declining to 8.13±2.30 cm in the second year. Correlation of the treatment response with age at treatment initiation, bone age delay and MPH was not significant.

**Conclusion:** It was found that the growth velocity was significantly increased after one year of treatment. The study provides long term follow-up and response to rGH Treatment (rGHT) in Indian children enrolled under ESIC scheme, however, prospective studies with large sample size and longer follow-up duration, which can report final height outcomes are needed.


**Keywords:** Height, Idiopathic, Mid parental height, Pituitary hormone deficiency

## INTRODUCTION

Short stature is defined as height less than 2 Standard Deviation (SD) for that age and sex. Short stature is one of the most common cause for referral to a paediatric endocrinologist. Short stature affects approximately 2-3% children in a given population [1,2]. Physiological causes like familial short stature and constitutional delay of growth and puberty are the two main causes of short stature, while GHD is relatively less common, but important, as it is a treatable cause of short stature. The prevalence of Growth Hormone Deficiency (GHD) among children with short stature is estimated to vary between 2.8% and 69%, and is predicted to be much higher in children postneurosurgical interventions [3].

The rGHT has shown to improve auxological outcomes in children with GHD [4,5]. Various Indian studies on growth hormone therapy have shown significant improvement in height velocity in the first year of treatment (8-10 cm), however the data is limited by small sample size, short follow-up duration and inclusion of heterogenous patient population [6-10]. In a developing country like ours, there is also lack of awareness and delay in diagnosis due to unavailability of hormonal tests and proper follow-up. There is also frequent discontinuation of treatment due to the high cost and need for prolonged therapy to measure the final outcome, in terms of difference in predicted adult height and final height.

With this background and due to the lack of availability of data from an Indian setting, the study was planned to evaluate the effect of rGH in children with short stature, who were enrolled under ESI Scheme. Under this scheme, they are eligible for free investigations and hormonal treatment, which ensures better compliance and follow-up.

## MATERIALS AND METHODS

This is a retrospective observational study in which children, who received rGHT from July 2016 to July 2020 in Pediatric Endocrine Clinic of ESI PGIMSR Basaidarapur, New Delhi, India, were enrolled. As per protocol, all the children coming to Paediatric Endocrine Clinic for short stature evaluation were initially investigated, to rule out systemic causes and other normal variants of short stature and were followed for a minimum of one year for growth velocity. They were then subjected to Growth Hormone Stimulation Test (GHST) after ensuring normal thyroid levels and ruling out systemic causes of short stature. Ethical clearance was taken from the Institutional Ethical Committee (ESIPGIMSR-IEC/20180052).

**Inclusion criteria:** Subjects diagnosed to have GHD and other causes for which growth hormone was indicated were enrolled, if they received treatment for two years, without discontinuation for more than one week.

**Exclusion criteria:** All those subjects whose follow-up was not adequate (3-4 monthly) or had discontinued treatment for more than one week, were excluded from the study.

### Study Variables

**Auxological parameters:** Height was measured to the nearest 0.1 cm by Harpenden stadiometer, at the start of GH treatment and then every three monthly, till continuation of treatment. Height was expressed as SD according to the formula: Height SD= (Measured height-Mean height for age)/SD for age. All measurements were made by skilled staff with participants dressed in minimal light clothing and without footwear. The stadiometer was calibrated using standard height. The Indian Academy of Paediatricians (IAP) growth charts

and standards were used across all ages for the above auxological parameters. Mid-Parental Height (MPH) was computed based on height of the parents (father's height+mother's height)/2, +6.5 cm for boys and -6.5 cm for girls). Pubertal assessment was done by Tanner Staging. Bone age was calculated using Greulich WW and Pyle SI Atlas at the start of treatment and in follow-up [11].

**Diagnosis of Growth Hormone Deficiency (GHD):** The GHD was diagnosed by GHST with either clonidine or glucagon. A peak serum GH level >10 ng/mL on GHST was considered as normal, excluding GHD. A peak serum GH level <5 ng/mL was taken as confirmatory for GHD, whereas for values between 5-10 ng/mL, a repeat GHST was done with injection glucagon/oral clonidine. A peak serum GH level <10 ng/mL in second GHST was taken as GHD [12].

All subjects underwent evaluation for other pituitary axis using appropriate hormone assays (serum T4, TSH, 8:00 am serum cortisol, plasma ACTH). 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 IGHD. In defining idiopathic short stature for the indication of recombinant human Growth Hormone (rhGH) treatment, the US Food and Drug Administration approved criterion of height -2.25 SD below the mean was taken [13].

**Hormone assay:** Growth hormone assay was done using chemiluminescent tracer-based immunometric assay (sandwich assay) using auto-analyser, in which a chemiluminescent molecule is used as an indicator label to detect and quantify immunological reactions.

**Treatment with growth hormone:** rGH (Norditorpin or genotropin) was initiated at a dose of 0.20-0.30 mg/kg/week [13]. Subjects were followed at 3-4 months interval for assessment of anthropometric and pubertal parameters, and for monitoring of adverse effects. Dose was adjusted on the basis of insulin-like Growth Factor-1 (IGF-1) levels and auxological parameters. If the growth velocity was below the normal range after starting GH (atleast three months) or if the IGF-1 levels were below 1SD for that age then the dose was increased, and IGF maintained between 1-2 SD. The gain in height and height SDs was measured, at the end of first year and subsequently in the second year.

## STATISTICAL ANALYSIS

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 21.0. Data were presented as number (%), mean (±SD) or median Interquartile Range (IQR) if the data was skewed. Quantitative variables following normal distribution were compared using Student's t-test and those that did not follow normal distribution were compared using Wilcoxon's rank-sum test. A p-value of <0.05 was considered statistically significant.

## RESULTS

The present study included data of 27 children (19 males and eight females) with short stature, being treated for minimum of 2 years with rGH. The mean age at treatment initiation was 9.85±3.04 years, with 20 of them being in peripubertal or pubertal age group (more than eight years). The most common aetiology for which the hormone therapy was started was IGHD (15/27, 55.5%), while the second most common indication was MPHD (18.5%, 5/27). [Table/Fig-1] illustrates the mean age of diagnosis for the various aetiology and change in height with growth hormone treatment. The mean height and height SD at baseline was 111.76±17.40 cm and -3.85±1.19 (-6.0 to -1.5), respectively. The mean bone age delay (chronological age-bone age difference) was 40.96±25.58 months.

The baseline height velocity was significantly lower, as compared to first and second year of treatment. The height velocity response was maximum during the first year of treatment (8.74±2.59 cm), declining to 8.13±2.30 cm in the second year, however, the difference in height velocity between the two years was not statistically significant. One

| Parameters | IGHD (n=15) | MPHD (n=5) | SGA (n=3) | Others (n=4) |
|---|---|---|---|---|
| Age at diagnosis (years) Mean (±SD) | 10.34±3.09 | 8.92±4.40 | 8.52±1.33 | 8.53±1.33 |
| Change in height Sd Mean (±SD) | 3.99±1.08 | 4.49±1.67 | 2.74±0.13 | 3.36±0.94 |
| Height velocity at diagnosis (cm) Mean (±SD) | 2.81±1.32 | 3.32±1.19 | 4.00±0.000 | 3.57±0.72 |
| 1st year height velocity (cm) Median (IQR) | 8 (6.2-11.5) | 7.5 (6.1-13.0) | 8.0 (7.5-) | 8.0 (8.0-9.9) |
| Second year height velocity (cm) Median (IQR) | 7.5 (6.0-10.0) | 8.5 (6.95-9.25) | 7.0 (6.5-) | 7.0 (5.5-8.95) |
| Delay in bone age (months) Median (IQR) | 37.0 (17-56) | 36 (26-61.5) | 31 (10-) | 44.5 (10.3-85.50) |

**[Table/Fig-1]:** Mean age at diagnosis and gain in height after treatment.
IGHD: Idiopathic growth hormone deficiency; MPHD: Multiple pituitary hormone deficiency; SGA: Small for gestation

factor repeated measures Analysis of Variance (ANOVA) revealed a significant change in velocity over the time. Mean height SDs also showed a significant change from baseline to first and second year of treatment. Pair-wise Bonferroni adjusted p-value are presented in [Table/Fig-2].

| Height velocity (cm) | | | p-values |
|---|---|---|---|
| **Baseline (1)** | **1st year (2)** | **2nd year (3)** | 1 vs 2=**p<0.001**<br>1 vs 3=**p<0.001**<br>2 vs 3=p=0.776 |
| 3.15±1.18 | 8.74±2.59 | 8.13±2.30 | |
| **Mean height SDs** | | | |
| **Baseline (1)** | **1st year (2)** | **2nd year (3)** | **p-values** |
| -3.85±1.19 | -3.17±0.98 | -2.51±0.90 | 1 vs 2=**p<0.001**<br>1 vs 3=**p<0.001**<br>2 vs 3=**p<0.001** |

**[Table/Fig-2]:** Height velocity before treatment and after treatment.
Bold p-values are statistically significant

Height velocity in first year was negatively associated with age at initiation of treatment (p=0.042; ρ=-0.395) [Table/Fig-3]. However, multiple linear regressions did not find significant association between height velocity at first and second year with bone age delay and MPH.

| Parameters | Spearman's correlation (ρ) and p-value | |
|---|---|---|
| | Height velocity in first year | Height velocity second year |
| Age at treatment initiation | ρ=-0.395; **p=0.042** | ρ=0.099; p=0.623 |
| Bone age delay | ρ=0.077; p=0.704 | ρ=0.150; p=0.454 |
| MPH | ρ=0.000; p=0.999 | ρ=0.271; p=0.172 |

**[Table/Fig-3]:** Correlation of treatment response with various baseline parameters.
MPH: Mid-parental height

## DISCUSSION

The present study presents the data of 27 children, who got growth hormone treatment without interruption for atleast two years. Data on such therapy is sparse in Indian literature due to the high cost and lack of easy availability. However, this was possible as all patients were ESI beneficiary and thus, entitled for free investigations and treatment.

In the present study, there was significant improvement in mean height SDs from -3.85±1.1 to -3.17±0.98 after one year treatment and -3.17±0.98 to -2.51±0.90 in the second year. The height velocity was maximum (8.74±2.59) in the first year of treatment. This is in accordance with most of the studies, which also showed that the height velocity response was maximum during the first three years after treatment initiation, followed by a graded decline over the subsequent years [6-10] [Table/Fig 4]. Mean height at presentation in the present study was 115.7±17.5 cm, which is similar to other Indian studies [7,8].

| Author and year | Age at treatment initiation (years) | Baseline height SDs (mean±SD) | First year height velocity (cm/year) | Follow-up (years) |
|---|---|---|---|---|
| Kannan V and Usharani K 1991 [7] | 2-14 (Range) | -3.8±1.1 | 10.9±2.2 cm/year | 5 |
| Menon PSN et al., 1991 [10] | 9.43±7 (mean±SD) | -2.5±1.3 | 8.0±2.2 cm/year | 1 |
| Bajpai A et al., 2006 [9] | 9.9±3.7 (mean±SD) | -4.8±1.6 | 10.3±2.9 cm/year | 1-9 |
| Khadilkar VV et al., 2007 [8] | 122.±8 (mean±SD) | -5.1±0.78 | 12.1±2.8 cm/year | 1 |
| Garg MK et al., 2010 [6] | 10.0±3.2 year (mean±SD) | Ht SDs: N/A Ht: 115.7±17.5 cm HA: 6.9±2.8 year | 8.7±2.7 cm/year 9.8±2.9 cm/year in GHD group | 3 |
| Present study | 9.85±3.04 years (mean±SD) | -3.85±1.19 | 8.74±2.59 | 2 |

**[Table/Fig-4]:** Comparison between the various Indian studies done on growth hormone and its outcome and duration of follow-up and treatment given [6-10].

The most common indication for GHT in the present study was primary IGHD. This is in accordance with most of the studies on growth hormone, where most common indication for growth hormone therapy is IGHD [6,14]. Mean age of treatment initiation was 9.85±3.04 years, as seen in most of the studies in India [6,12], due to lack of awareness and late presentation. However, the mean age at presentation was lower in patients with systemic diseases, as compared to IGHD, though not statistically significant, as they were brought to medical attention, earlier due to their primary illness. Bone age deficit in this study was 40.96±25.58 months, which is also comparable to another study [9].

The present study shows significant correlation between first year change in height velocity and age at initiation of treatment, however, there was no correlation between MPH or bone age delay. Whereas, Gahlot M et al., showed significant negative correlation 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 [12]. The difference is probably due to the small sample size in the present study. Thus, in clinical practice, these could serve as important predictors of first year response, to growth hormone treatment. The strength of the present study is that, there was no discontinuation of treatment and better compliance, since the treatment was given free of cost and the dose could be increased according to the needs without any financial constraints.

### Limitation(s)

The study was retrospective in nature with a small sample size and follow-up data was there for two years only.

## CONCLUSION(S)

The present study provided data to reflect the response to rGHT among Indian children. There was a significant improvement in the height velocity in the first two years. There is also significant negative correlation between age of initiation and first year height velocity after initiating treatment. However, prospective studies with large sample size and longer follow-up duration, which can report final height outcomes are needed in the near future.

## 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(6):820-22.
[2] Bramswig JH. Short and tall stature. Ann Nestle Eng. 2007;65(3):117-27.
[3] John M, Koledova E, Kumar KMP, Chaudhari H. Challenges in the diagnosis and management of growth hormone deficiency in India Int J Endocrinol. 2016;2016:2967578. Doi: 10.1155/2016/.
[4] 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(2):418-206.
[5] 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(6):2047-54.
[6] Garg MK, Pakhetra R, Dutta MK, Gundgurthi A. Response to growth hormone therapy in Indian patients. Indian J Paediatr. 2010;77(6):639-42.
[7] Kannan V, Usharani K. Human growth hormone therapy: Long term responses in 30 children with growth hormone deficiency. Indian J Paediatr (Suppl). 1991;58:65-69. Doi: 10.1007/BF02750986.
[8] Khadilkar VV, Khadilkar AV, Nandy M, Maskati GB. Multicentric study of efficacy and safety of growth hormone use in growth hormone deficiency. Indian J Pediatr. 2007;74(1):51-54.
[9] Bajpai A, Kabra M, Gupta AK, Menon PSN. Growth patternand Skeletal maturation following growth hormone therapy in growth hormone deficiency: Factors influencing outcome. Indian Paediatr. 2006;43(7):593-99.
[10] Menon PSN, Virmani A, Sethi AK. Biosynthetic growth hormone therapy in children with growth hormone deficiency: Experience at AIIMS, New Delhi. Indian J Paediatr. 1991;58(Suppl 1):71-77.
[11] Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. Stanford: Stanford University Press; 2011.
[12] Gahlot M, Goyal A, Singh AK, Jyotsna VP, Gupta N, Khadgawat R. Long-term response to recombinant human growth hormone therapy in Indian children with growth hormone deficiency. Indian J Endocr Metab. 2019;23(4):446-51.
[13] Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: A summary of the growth hormone research society, the Lawson Wilkins Paediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. The Journal of Clinical Endocrinology & Metabolism. 2008;93(11):4210-17.
[14] Wilton P, Wallstrom A. An overview of the diagnosis in the Kabi Pharmacia International Growth Study. Acta Paediatr. 2008;80:93-98. Doi: 10.1111/j.1651-2227.1991.tb12053.x.



**PARTICULARS OF CONTRIBUTORS:**
1. Associate Professor, Department of Paediatrics, ESI PGIMSR, Basaidarapur, New Delhi, India.
2. Assistant Professor, Department of Paediatrics, ESI PGIMSR, Basaidarapur, New Delhi, India.
3. Professor and Head, Department of Paediatrics, ESI PGIMSR, Basaidarapur, New Delhi, India.
4. Statistician, Department of Statistics, AIIMS, New Delhi, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Smriti Rohatgi,
D-72, Ground Floor, Hauz Khas, Delhi, India.
E-mail: rohatgi.smriti@gmail.com



**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Oct 04, 2022
- Manual Googling: Dec 01, 2022
- iThenticate Software: Dec 05, 2022 (12%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 03, 2022**
Date of Peer Review: **Oct 27, 2022**
Date of Acceptance: **Dec 06, 2022**
Date of Publishing: **Feb 01, 2023**