Response to Recombinant Human Growth Hormone (rhGH) Therapy in Children with Growth Hormone Deficiency

Maira Riaz[1], Mohsina Noor Ibrahim[1], Versha Rani Rai[1], Safia Bibi[2], Zubair Ahmed Khoso[1] and Taj Mohammad Laghari[1]

[1]*Department of Paediatric Endocrinology, National Institute of Child Health, Karachi, Pakistan*
[2]*NIH-Health Research Institute, Research Centre NICH, Karachi, Pakistan*

ABSTRACT

Objective: To determine the auxological response to recombinant human growth hormone (rhGH) therapy in children with growth hormone deficiency (GHD) presenting at the National Institute of Child Health, Karachi, Pakistan.

Study Design: Observational study.

Place and Duration of the Study: Department of Paediatric Endocrinology, National Institute of Child Health, Karachi, Pakistan, from January 2022 to December 2023.

Methodology: All pre-pubertal children with short stature aged 3-12 years diagnosed with GHD and who were prescribed rhGH therapy were included in the study. Children with any other underlying reason for short stature or any other comorbidity were excluded. Patients' demographics and baseline growth parameters were recorded in a pre-designed proforma. Patients were then followed up every three months till one year. Response to rhGH therapy was evaluated through comparison of growth parameters before and after one year of therapy.

Results: A total of 90 children including 47 (52.2%) males and 43 (47.8%) females with GHD were enrolled. Mean age of these patients was 7.92 ± 2.647 years. A statistically significant change in height (SD), Weight (SD), and BMI (SD) was observed before and after one year of therapy ($p < 0.001$). Response to therapy in terms of height did not differ significantly with respect to gender ($p = 0.955$) or stimulated growth hormone levels ($p = 0.911$). However, response to rhGH therapy was significantly better in terms of increase in height, weight, and BMI in patients presenting earlier i.e. at age ≤8 years.

Conclusion: Recombinant human growth hormone therapy was effective in children with short stature to achieve desirable growth. Children diagnosed and treated at a younger age (≤8years) achieve better height outcomes as compared to those presenting late.

Key Words: *Short stature, Growth hormone deficiency, Recombinant human growth hormone.*

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INTRODUCTION

Growth hormone deficiency (GHD) is regarded as a common reason in children with short stature. According to Official Federal Statistics of Russian Population (OFMS), the prevalence of GHD among children is 1:6950. The seven high expenditure disease (7HED) registry shows almost similar results.[1] Data of 430 children with GHD from Bombay, India proved that 31% of the children had familial GHD and about 17% of children had idiopathic GHD.[2]

Correspondence to: Dr. Maira Riaz, Department of Paediatric Endocrinology, National Institute of Child Health, Jinnah Sindh Medical University, Karachi, Pakistan
E-mail: mairariaz@yahoo.com

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A study from Pakistan reported GHD as the third (10.7%) most common cause of short stature in children after familial short stature (21.3%) and hypothyroidism (17.2%).[3] Another study from Pakistan showed GHD prevalence to be 23% among short children preceded by constitutional and familial short stature.[4]

In 1985, recombinant human growth hormone (rhGH) therapy was approved for children with GHD.[5] Replacement therapy with rhGH in children with GHD is reported to be effective in gaining catch-up growth (CUG) in the first year of treatment, followed by a maintenance period and ultimately reaching to a height close to the target adult height.[6]

Several studies claim that after one year of rhGH therapy (0.03-0.05 mg/kg/day), the height (SD), weight, and body mass index (BMI) increase significantly in growth hormone-deficient children.[7,8] However, the response to growth hormone treatment varies among different populations.[9] In the United States and Europe, the height standard deviation (SD) score of adult

height after treatment is higher than that in Japan.[10] Also, a sizeable fraction of children is reported who fail to gain this initial response and end up in compromised adult height.[11-13]

Being an expensive treatment, data on the efficacy of rhGH therapy from developing countries such as Pakistan are very scarce. In Pakistan, recently a study from a tertiary hospital of the country showed improvement in growth parameters[14] and another study evaluated the factors leading to non-adherence to growth hormone therapy.[15] But none of these studies identified the relation of change in height (SD) with factors, such as age at initiation of therapy, pretreatment (SD), and comparison between partial and complete GH deficient groups. The aim of the present study was to assess the response to rhGH therapy in terms of auxological parameters and factors that contribute to the good response to the therapy after one year of treatment.

METHODOLOGY

This observational study was conducted at the paediatric endocrinology unit of the National Institute of Child Health, Karachi, Pakistan, from September 2022 to 2023 after obtaining Institutional Ethical Review Board approval (IERB no: 30/2022). Written informed consent was obtained from the parents of all patients before enrolment. A sample size of 90 patients with GHD was calculated using OpenEpi sample size calculator at 95% confidence level and 6.5% margin of error on the basis of a study that documented 89% of patients with GHD yield desirable auxological response to growth hormone therapy.[15]

During the study period, all pre-pubertal children aged 3-12 years diagnosed to have GHD on the basis of provocative test (insulin tolerance test) and prescribed rhGH therapy were enroled in the study. Their thyroid functions, IGF1 level, baseline complete blood count, and biochemistry including creatinine, alanine aminotransferase (SGPT), serum electrolytes, and fasting sugars were all done before including them in the study to rule out other possible causes of short stature. Patients with other possible cases of short stature were excluded. A complete physical examination and growth assessment were carried out, including height, weight, and BMI, with their SDs according to chronological age and recorded in a predesigned proforma prior to the start of growth hormone therapy.

Treatment with rhGH was then initiated at a dose of 0.02 mg/kg/day subcutaneously 6 days a week, after full description and counselling about the administration technique and possible side effects. Patients' attendants were advised to self-inspect the injection site regularly. The adherence to treatment was reassured by examining the injection sites by the attending physician every other month in the hospital's growth clinic.

These children were then followed up on every three months. A dose of rhGH was adjusted on every visit according to weight and patients were inquired for any possible adverse effects like injection site pain or headache etc. The increment in height in terms of height velocity (change in height in cm/year) was recorded after 12 months of growth hormone treatment.

Data were analysed using Statistical Package for Social Science (SPSS) version 24.0. Frequencies and percentages were reported for qualitative variables. Median (IQR) or mean ± SD as appropriate were reported for quantitative variables after normality testing using Shapiro-Wilk's test.

Paired sample t-test was used for comparing pre- and post-treatment weight and BMI as these were normally distributed. Wilcoxon Signed-Rank test was used to compare pre- and post-treatment data for variables which were not normally distributed i.e. height, weight (SD), height (SD), and BMI (SD). Student's t-test for independent variables and Mann-Whitney U test were used to compare treatment response with respect to gender, age (<8 years and >8 years), and GH deficiency i.e. complete or partial deficiency. A p-value less than 0.05 was considered significant in all statistical analyses.

RESULTS

A total of 90 children including 47 (52.2%) males and 43 (47.8%) females with GHD were registered in the study. Mean age of these patients was 7.92 ± 2.647 years with the youngest child presenting at 3 years of age to the eldest presenting at 12 years of age. Patients were categorised into two groups with respect to age which included 50 (55.6%) patients who presented at the age of up to 8 years while 40 (44.4%) patients presented after 8 years of age. (Median age: 8 years (IQR1: 6, IQR3:10).

Of the total 90 children with GHD, 54 (60%) children had complete GHD with a peak growth hormone level <5ng/dl, while 36 (40%) patients had partial GHD with a peak growth hormone level between 5-10 ng/dl.

Table I shows the response to growth hormone therapy after one year of growth hormone therapy which depicted that there was a statistically significant increase in the mean / median values of all observed auxological parameters including height, weight, BMI, height (SD), weight (SD), and BMI (SD) ($p < 0.05$).

Comparative analysis of treatment response with respect to gender revealed that there was no statistically significant difference in terms of median change in height standard deviation (Ht. SD), median change in weight (SD) or mean change in BMI (SD) ($p = 0.955, 0.671$, and 0.415, respectively).

Table I: Comparative analysis pre- and post-treatment auxological parameters in patients with GHD.

	Pre-treatment Mean ± SD / median (IQR)	Post-treatment Mean ± SD / median (IQR)	p-value
Height	105.05 (92.75 – 113.0)	109.00 (99.25 – 117.0)	<0.001*
Weight	16.853 ± 5.595	19.288 ± 5.570	<0.001**
BMI	15.911 ± 2.505	16.851 ± 2.591	<0.001**
Height (SD)	-4.365 (-5.395 – -3.523)	-3.85 (-4.955 – -3.19)	<0.001*
Weight (SD)	-3.74 (-4.767 – -2.68)	-2.810 (-3.997 – -2.265)	<0.001*
BMI (SD)	-0.120 (-1.438 - 0.645)	0.020 (-0.835 - 0.8100)	<0.001*

** Wilcoxon Signed-Rank test ** Paired t-test.*

A comparison of treatment response with respect to partial or complete GHD also revealed that the median change in height (SD), median change in weight (SD), and mean change in BMI (SD) after therapy did not differ significantly (p = 0.911, 0.581, and 0.819, respectively) between patients with partial or complete GHD.

Data stratification with respect to age categories i.e. less than 8 or more than 8 years of age showed that median change in height (SD) after therapy was not significantly different between patients younger than or more than 8 years of age (p = 0.363). However, the median change in weight (SD) and mean change in BMI (SD) was significantly different (p <0.001) between the two groups. These results reflect that response to growth hormone therapy was significantly better in terms of increase in weight (SD) and BMI (SD) in patients presenting earlier i.e. at age ≤8 years.

Regarding any side effects, the patients had only few occasional complaints of injection site pain and headache. These adverse events being mild did not result in dropouts from the treatment.

DISCUSSION

The present study is the first prospective study from Pakistan that highlights the data on growth hormone treatment response after a complete year of uninterrupted therapy. Results indicated a considerable increase in measured growth parameters (weight, height, and BMI) in all age groups after treatment. This is similar to many studies worldwide that prove significant improvement in height (SD) and growth velocity after treating GHD kids and adolescents with GH.[1,6,8,11] An earlier study from Pakistan also compared the mean scores of growth velocity at 6th and 12th month among 87 participants and showed considerable improvement.[15]

The mean age of study participants was 7.84 years (from the youngest child at 3 years to the oldest presenting at 12 years of age). The mean age of presentation is very much different among local and international data.[6] In the past years, the mean age of presentation was reported to be early teens and hence treatment was commenced on higher ages.[16,17] This difference can be due to better awareness about stature and availability of referral centres nowadays.

Study results were analysed with respect to age categories in below and above 8 years' age group (50 and 40, respectively) to investigate the impact of age of presentation on response to rhGH therapy. Results were statistically not significant (p = 0.086) but the mean change in height (SD) was more in the younger age group (<8 years) as compared to the older group (>8 years). There are many studies that proved better results in terms of improvement in height (SD) if treatment had started earlier.[16,18,19] Height at the beginning of therapy is particularly considered a key variable affecting the final outcomes; hence, smaller children are expected to achieve better CUG in the GHD population.

In present study there were more males than females who were brought to seek medical advice for GHD similar to the available data from other studies.[15,16,20,21] However, it is difficult to interpret whether males are predominantly affected by GHD or if it is because of the health-seeking behaviour. Present study did not show any difference in terms of rhGH therapy response with respect to gender which is in concordance with other studies.

Severe GHD (<5ng/dl) was observed in the majority of this study's participants which is similar to other local data available.[14] This is also similar to other neighbouring countries where mean peak growth hormone level is reported to be 6.51 ± 1.41 ng/ml in a cohort of 150 growth hormone deficient patients.[20] Comparative analysis between children with complete or partial GHD did not show any significant difference in height (SD) after one year of GH therapy. This is in concordance with the study by Yoon *et al*.[19] This suggests that decision regarding growth hormone therapy should not be affected by the severity of GHD as patients with partial deficiency exhibit similar responses as those with severe deficiency. However, previous literature shows conflicting results in considering peak growth hormone as a predictor of growth response.[19]

The limitation of the present study is that the authors could not perform baseline IGF-1 level in all patients due to financial constraints. Long-term follow-up study to assess the effect of GH on final adult height in children with GHD is recommended. Also, the side effects after prolong use of GH can be assessed if administration is continued till the desired height is achieved. However, currently it is considered to be a costly therapy and many families find it very difficult to continue it in resource-limited countries like Pakistan.

CONCLUSION

rhGH is an effective and safe preparation in the replacement therapy for children with GHD that can help children with short stature to achieve desirable growth. It is important to identify and treat children with GHD earlier to achieve better height outcomes.

ETHICAL APPROVAL:

Ethical approval was obtained from Institutional Ethics Review Board of the National Institute of Child Health, Karachi, Pakistan before the commencement of the study (IERB no: 30/2022).

PATIENTS' CONSENT:

Written informed consent was obtained from the parents of all patients before enrolment.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MR, MNI: Conceptualisation, data collection, and manuscript drafting.
VRR, ZAK, TML: Data collection.
SB: Study design, data analysis, and manuscript drafting.
All authors approved the final version of the manuscript to be published.

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