## *Brief Reports*

# Growth Hormone in Turner Syndrome

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*Manuscript received: May 12, 2005, Initial review completed: June 24, 2005; Revision accepted: September 23, 2005.*

*We assessed the effect of one year of therapy with recombinant Human Growth Hormone (rhGH) on growth velocity of 16 Indian girls with Turner Syndrome (TS) in a prospective, open trial. Patients received rhGH in a dose of 1 IU (0.3 mg)/kg/week. The mean pretreatment height was 117.1 cms (Z score –3.4), height velocity was 3.8 cm per year (Z score –2.4), and predicted height was 140 cm. At the end of therapy mean height was 123.9 (Z score –3.1), height velocity was 6.7 cm per year (Z score + 1.7), and the predicted height was 142.4 cm. The increment in height velocity with growth hormone therapy was statistically significant (P value = 0.001) and the mean increment in predicted height was 2.4 cm. Our study shows that girls with TS in India benefit from therapy with rhGH.*

**Key words:** *Growth hormone, Height velocity, Turner syndrome.*

**TURNER** syndrome occurs due to a complete or partial absence of the second X chromosome in girls and is characterized by short stature, female phenotype, sexual infantilism and somatic abnormalities(1). It is seen approximately in 1 in 2000 female live births. Short stature is seen in more than 95% of patients with Turner syndrome (TS) and they are likely to have a mean adult height of up to 20 cm less than that of the general female population(2). As such a significant focus of medical management in TS is on growth promoting strategies. In recent years a number of studies have indicated that the administration of recombinant Human Growth Hormone (rhGH) can increase the growth velocity of girls with TS(3). We report here the results of a study where 16 girls with TS were treated with rhGH for a period of one year.

## Subjects and Methods

A prospective, open label trial with rhGH was performed at five centers in 16 girls with TS who had never received rhGH. The diagnosis of TS was confirmed by Karyotype. Chronological age of the girls ranged from 7.2 to 17.1 years (mean 11.1 years) and skeletal age ranged from 4.9-13.5 years (mean 9.4 years). The ethics committee of all the hospitals approved the study and informed consent was obtained from all parents. The inclusion criteria–girls with confirmed diagnosis of TS, with a height of <–2 standard deviation (SD) below the population mean, having at least one previous height reading within the past 3 months, euthyroid status (or

controlled on medication). Patients with known Growth Hormone resistance, or any abnormality likely to affect growth or its evaluation such as renal insufficiency were excluded. Height was recorded using a Child Growth Foundation Stadiometer to the accuracy of 1 mm, while weight was recorded on a Salter electronic scale to an accuracy of 100 grams.

At enrollment height, weight, parent's height, previous height measurement, pre-existing conditions and concomitant medications were recorded. A detailed physical examination was performed, an *X*-ray of the non dominant wrist and hand for bone age was taken and blood was drawn for a hemogram, fasting blood glucose, glycosylated hemoglobin, calcium, phosphorous, alkaline phosphatase, serum electrolytes, blood urea, serum creatinine, AST, ALT, free T4 and free T3, thyroid stimulating hormone (TSH) and insulin like growth factor 1 (IGF-1).

All patients received growth hormone in a dose of 1 IU (0.3 mg/kg/week) given as seven divided doses as subcutaneous daily injection at night. Growth hormone was provided by LG lifesciences (Eutropin) as 4 IU vials. The 4 IU vial contains 1.33 mg of lyophilized recombinant rhGH protein and a separate vial contains 1 mL solvent for solution. The protein consists of 191 amino acid residues and is produced from genetically engineered yeast cells of the strain Saccharomyces cerevisiae. All patients were asked to maintain a diary and missed doses, local and systemic reactions were recorded. Height and weight measurements were performed again at 6 months and at the end of one year of therapy. Blood investigations were repeated after one year of therapy. All sixteen patients completed the one-year study period.

Data analysis was performed using Microsoft excel 2000 data analysis pack. Height, weight, height velocity, body mass index (BMI), mid parental height (MPH) and IGF-1 were expressed as standard deviation scores (Z scores)(4,5). TW3 RUS method was used for calculating the bone age and predicted height of children based on their current age, height and RUS score(7). Student's *t*-test was used to compare the difference between means.

## Results

Of the 16 patients studied, five had a Karyotype of 45 XO, eight were 45X/46XX and three were 45XX (iXq) and none of the girls showed signs of puberty. The mean pretreatment parameters are depicted in *Table I.* At the beginning of the treatment, all patients thyroid function, creatinine, hemoglobin, electrolytes, blood sugar, glycosylated hemoglobin, calcium, and liver function tests were normal and were free from any major systemic disease except the abnormalities associated with Turner syndrome. The associated conditions were scoliosis and kyphoscoliosis, squint, horseshoe kidney, coarctation of aorta, lymphedema, anemia, difficulty in mathematics at school and one patient developed hypothyroidism while on treatment with rhGH. One patient reported urticaria during the first month of therapy, which subsided without anti-allergy treatment. No other local or systemic reactions possibly occurring due to growth hormone administration were noted.

Post-treatment parameters at the end of one year of therapy are listed in *Table I.*

The mean increment in bone age was 1year at the end therapy. The increment in height velocity with growth hormone therapy was statistically significant (P = 0.001) (*Fig.1*). Patient's height had a strong correlation with the mid-parental height (correlation

**TABLE I–***Growth Parameters in Children with Turner's Syndrome Before and After Therapy.*

| Parameter | Pretreatment | Post-treatment |
|---|---|---|
| Age (years) | 11.1 (2.8) | 12.1 (2.8) |
| Height (cm) | 117.1 (11.5) | 123.9 (11.3) |
| Height velocity (cm/year) | 3.8 (1.3) | 6.8 (1.4) |
| Weight (kg) | 22.6 (7.7) | 25.8 (8.6) |
| BMI (kg/m$^2$) | 16.1 (2.6) | 16.4 (2.9) |
| Bone age (years) | 9.6 (2.9) | 10.6 (2.8) |
| Height Z score | –3.4 (1.1) | –3.1 (1.2) |
| Height velocity Z score | –2.4 (2.5) | +1.7 (2.4) |
| Weight Z score | –1.5 (0.7) | –1.4 (0.9) |
| BMI Z score | –0.4 (2.9) | –0.5 (0.9) |
| Predicted height | 140.0 (6.4) | 142.4 (7.0) |

All values are expressed as mean (SD).

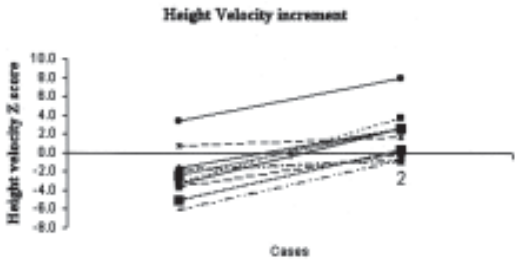


*Fig. 1. Improvement in height velocity in 15 patients with Turner syndrome while on a year of therapy with Growth hormone.*

coefficient = 0.7). The mean increment in predicted height at the end of therapy was 2.4 cm. The mean alkaline phosphatase was 381.1 U/L at start of therapy and rose to 543 after one year of therapy. The IGF-I Z scores rose from -0.6 to + 2.5 and the difference was statistically significant (P = 0.03).

Using Ranke's data for girls with Turner Syndrome the pretreatment height Z score of our Turner girls was –1.1, and after treatment it was –0.51(8). The pretreatment height velocity Z score as compared with Ranke's data was +0.55 while after treatment with growth hormone this was + 4.31.

## Discussion

The diagnosis of TS should be suspected in any girl who presents with unexplained short stature, even in the first 3 years of life(9). The exact etiology of short stature in TS is still a subject of speculation and the hypotheses include a gene located in the pseudoautosomal region (PAR 1) at the tip of the short arm of the X chromosome (Xp 22.3), global genetic factors, and lack of pubertal growth(10,11). A strong correlation between TS patients' height and mid-parental height (MPH) has been confirmed in several studies(11,12).

Clinical trials of recombinant rhGH therapy have shown that rhGH accelerates the linear growth rate. In a landmark trial Rosenfeld, *et al.*(13) who followed their patients until the age of 17-18 (near final height) showed that patients treated with rhGH gained 8.5 cm over their projected final height. These and other similar studies have shown that a final height of 150 cm is an achievable goal in TS girls with the use of rhGH. Growth

**Key Messages**

- Short stature is seen in more than 95% of patients with Turner syndrome and hence a significant focus of medical management in Turner Syndrome is on growth promoting strategies.
- Indian girls with Turner syndrome benefit from recombinant human growth hormone therapy demonstrating improved growth velocity and final height prediction.

Hormone treatment if started early, results in normalization of height during childhood and normalization of adult height in most of the girls treated with rhGH for a number of years(3). The recommended starting dose of rhGH is around 0.15 IU (0.05 mg/kg) per day which is higher than the dose used for children with Growth Hormone Deficiency. Growth hormone therapy is usually well tolerated. The potential untoward reactions are occurrence of benign intracranial hypertension, carbohydrate intolerance, edema, local reactions such as redness and itching, slipped capital femoral epiphyses and exaggeration of scoliosis(1).

In India the diagnosis of TS is often delayed not only because of a lack of expertise but also because the girl child is neglected and brought to the attention of medical help because of pubertal delay rather than short stature. Second major problem is the enormous cost of rhGH therapy, which is in the range of 3-5 lakh rupees/year.

In our study there was a significant increase in the height velocity during therapy showing that rhGH can stimulate short-term growth in patients with TS. The improvement in the predicted height after one year of rhGH therapy was 2.4 cm, similar to the improvement in predicted height shown in other studies(13). Western data suggests that TS girls have a higher BMI and are overweight as compared to the general population. We did not find this in our patients; this could be due to poor nutrition or a different phenotype. There was a mean increment of one year in the bone age during rhGh therapy confirming that growth hormone selectively promotes height growth without advancing bone age thus improving the final height. When a comparison was made between Indian TS girls and Ranke's TS standards our patients were generally shorter but were growing at normal speed for TS before treatment with rhGH was started.

Our study shows that Indian girls with Turner syndrome benefit from rhGH therapy, demonstrating improved short-term skeletal growth as well as improved final height prediction.

**Acknowledgements**

We thank Dr. Madhulika Kabra, Additional Professor, All India Institute of Medical Sciences, New Delhi, Dr. Mala Dharmalingam, Associate Professor, M.S. Ramaiah Medical College and Hospital, Bangalore, Ms. Deepa Lokhandi and the nursing and pharmacy staff of the respective hospitals for their valuable assistance in successful completion of the study.

We would also like to extend our sincere gratitude to LG Life Sciences India for their generous supply of human growth hormone.

*Contributors:* VVK and AVK carried out the clinical workup. AVK, MN and GBM collected and verified the data and drafted the manuscript. VVK will act as guarantor of the study.

*Funding:* LG Life Sciences India Pvt. Ltd., LG House, AB-3, Safdarjung Enclave, New Delhi 110 029 and HCJMRI, Jehangir Hospital, Pune.

*Competing Interests:* Financial support for the investigations and the growth hormone was provided by LG Life Sciences India Pvt. Ltd., at all centers. M Nandy, One of the authors, is also an employee of LG Life Sciences India Pvt. Ltd.

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