Growth Hormone Treatment in Turner's Syndrome: A Real World Experience

Vijay Sheker Reddy Danda, P. Sreedevi, G. Arun, P. Srinivas Rao

Department of Endocrinology, Gandhi Medical College/Gandhi Hospital, Musheerabad, Hyderabad, Telangana, India

Abstract

Objective: Short stature is a universal clinical feature of Turner's syndrome (TS). Growth failure begins in fetal life, and adults with TS are on an average 20 cm shorter than the normal female population. Since there is a paucity of data from India regarding the effect of growth hormone (GH) on TS patients, we retrospectively analyzed the data of TS patients who are on GH treatment. **Methods:** This hospital-based observational retrospective study was conducted in a tertiary care hospital of Hyderabad. The data such as height, weight, and bone age of 16 patients who are diagnosed with TS on GH therapy for at least 6 months were included in the study. All the patients were treated with human recombinant GH at the dose of 0.3 mg/kg/week administered as daily subcutaneous injections. **Results:** The mean age at diagnosis was 12.7 years. The mean height at the start of GH therapy was 1.26 m, and mean height standard deviation score (HSDS) was-0.61 when compared to Turner's specific reference data. With a mean duration of GH therapy of 25 months, the mean height at the end of therapy was 1.37 m and the mean height as per HSDS was + 0.37 resulting in a mean height gain of + 0.99 HSDS. **Conclusion:** Our observation shows that girls with TS benefit from early diagnosis and initiation of treatment with GH.

Keywords: Growth hormone, short stature, Turner's syndrome

INTRODUCTION

Turner's syndrome (TS) is one of the most common human genetic disorders, affecting approximately 1 in every 2500 live-born females.[1] Growth failure is a cardinal feature of TS, which may impair their quality of life,[2] and adult patients have a mean height approximately 20 cm lower than that of unaffected women of the same ethnic group.[3] Short stature results partly from haploinsufficiency of the short stature homeobox gene on the distal part of short arms of chromosome X, whereas the growth hormone (GH)/ insulin-like growth factor 1 axis is normal in these patients.

A variety of growth-stimulating therapies to increase the height of these patients include treatment with androgens (oxandrolone),[4] estrogens at a low dose,[5] and more recently, GH,[6] as well as a various combination of the above therapies. Several studies have shown that GH treatment increases adult stature in TS,[7] and this therapy is now approved by the United States Food and Drug Administration and other regulatory agencies worldwide.

However, there is a paucity of data from India, regarding the effect of GH on TS patients. Therefore, we present the study results of observational data of 16 patients from our institute treated with GH.

METHODS

The experience gained since 2003, through observation of case records of 16 girls with TS under GH treatment for at least 6 months or more were analyzed. Diagnosis was made on the basis of clinical phenotype, hormonal analysis, and confirmed by karyotypic analysis of a peripheral blood sample.

All patients underwent testing as a part of evaluation of short stature and/or delayed puberty. Serum follicle-stimulating hormone and luteinizing hormone were done in patients who

Address for correspondence: Dr. Vijay Sheker Reddy Danda,
Gandhi Medical College/Gandhi Hospital, Musheerabad,
Hyderabad, Telangana, India.
E-mail: drdvsreddyendo@yahoo.com

Access this article online

Quick Response Code:

Website:
www.ijem.in

DOI:
10.4103/ijem.IJEM_36_17

were 11 years of age or above. Karyotypic analysis of peripheral blood, thyroid function test, ultrasound examination of genitourinary system, two-dimensional echocardiography, and X-ray of the nondominant wrist and hand for bone age (BA),[8] apart from routine biochemistry and hemogram were done in all patients. None of the patients had spontaneous puberty. Patients' height was obtained by direct measurement on a wall-mounted stadiometer. The mid-parental height (MPH) was calculated as (father height + mother height)/2–6.5 cm. The target height range was defined as MPH ± 2 standard deviation (SD). The height SD score (HSDS) of patients was calculated based on the Turner's specific reference data described by Lyon *et al*.[9] [Table 1]. Body mass index (BMI) of patients at the start of GH treatment and at the end of GH treatment or at the time of data collection who were still on GH therapy was collected.

All the patients were treated with human recombinant GH at the dose of 0.3 mg/kg/week administered as daily subcutaneous injections. These patients had been on no fixed treatment protocols or any standard dose of GH. Estrogen treatment was initiated for the induction of puberty at varying ages. Investigations and ongoing surveillance were determined individually as needed.

The effect of GH treatment was evaluated by comparing the height at the start of therapy to height at the end of GH therapy or at least 6 months of GH therapy at the time of data collection. Second, HSDS was calculated at both the above-mentioned points using both Turner's specific reference data as described by Lyon *et al*.[9] and the national Agarwal *et al*. growth charts,[10] and the gain in HSDS due to GH therapy was calculated.

Results are expressed as mean ± SD height gain was correlated with variables known to effect height with Pearson's correlation coefficient. For confirming relationship, multiple regression analysis was used.

RESULTS

Sixteen patients with TS on GH treatment were studied. The mean age of diagnosis was 12.7 years, 11 patients had a karyotype of 45 × 0 were mosaic, and 3 had structural abnormalities. Associated abnormalities with TS included scoliosis, horseshoe kidney, Bicuspid aortic valve, atrial septal defect, coarctation of the aorta, and hypothyroidism [Table 2]. None of the girls showed signs of puberty.

GH was started at mean age of 12.7 years. The mean BA of 10.6 years was delayed in comparison to the chronologic age. However, there was no correlation between BA delay and HSDS at the start of therapy ($r = 0.334$, $P = 0.20$). The MPH was 1.53 m. At the start of GH therapy, the mean height was 1.26 m and mean weight was 32.6 kg with a mean BMI was 20.01. The mean HSDSs when compared to Turner's specific reference data derived from Lyon *et al*. was − 0.61 SDS.

The mean duration of GH therapy was 25 months. The mean height at the end of GH therapy was 1.37 m. The mean HSDS when using the Lyon data increased from − 0.61 at the start of GH therapy to + 0.37 at the end of study resulting in a HSDS gain of 0.99 over a mean of 25 months of therapy. Similarly, mean HSDS when compared to data derived from Agarwal *et al*. data was − 4.0 at the start of GH therapy and increased to − 3.37 at the end of GH therapy resulting in a gain of 0.63 SDS. There was a significant positive correlation between duration of therapy and gain in HSDS ($r = 0.534$, $P = 0.032$). However, on multiple regression analysis after adjusting for other factors, this was no longer significant.

Table 1: Baseline characteristics

n	Age at presentation (years)	Bone age (years)	MPH (m)	Height (m)	HSDS (Lyon *et al*.)[9]	Weight (kg)	BMI	BMI SDS (Agarwal *et al*.)[10]
1	9	9	1.51	1.07	−2	14	12.23	−2.30
2	14	12	1.52	1.34	0.2	32	17.82	−0.74
3	14	12	1.49	1.405	1.43	32	16.21	−1.74
4	15.8	10	1.44	1.26	−2.38	32	20.16	0.10
5	10	10	1.47	1.13	−1.4	20	15.66	−0.34
6	9	9	1.51	1.05	−2.44	12	10.88	−3.38
7	15.5	10	1.44	1.31	−1.24	35	20.40	0.48
8	13.3	10	1.52	1.26	−0.95	37	23.31	2.88
9	13	13	1.52	1.225	−1.5	38	25.32	4.20
10	12	9	1.54	1.32	1	46	26.40	5.37
11	15	13	1.61	1.36	0	56	30.28	6.65
12	14.5	11	1.59	1.38	0.67	33	17.33	−1.11
13	11.5	10	1.58	1.285	0.71	36	21.80	2.81
14	13.9	11	1.65	1.4	1.4	38	19.39	0.24
15	12	11	1.53	1.24	−0.6	39	25.36	4.72
16	11.6	11	1.56	1.12	−2.8	22	17.54	0.15
Mean	12.75	10.69	1.53	1.26	−0.62	32.62	20.01	1.12
SD	2.15	1.30	0.06	0.11	1.42	11.27	5.25	2.95

MPH: Mid parental height, HSDS: Height standard deviation score, SDS: Standard deviation score, BMI: Body mass index, SD: Standard deviation

The mean BMI and BMI SDS at the start of GH therapy was 20.01 and 1.12, respectively. The mean BMI and BMI SDS at the end of GH therapy was 20.96 and 1.08, respectively. The mean change in BMI SDS was −0.04 [Table 3].

They were no local or systemic reactions possibly occurring due to GH therapy except for bilateral tonsillar enlargement in two patients.

DISCUSSION

TS patients are about 20 cm shorter than the average adult female height of that country and considering the fact that the average height of Indian women is 1.52 m.[11] Our TS patients may be much shorter when compared to average Western adult Turner's height of 145 cm. However, final height of untreated TS patients is not available in this country. Long-term growth and final height after GH therapy in girls with TS are now available from several studies. Some studies have shown

only small gain in height,[12,13] while others claim significant improvement in height.[13,14] This discrepancy is likely to be due to several factors such as age at starting GH, dose of GH, age of sex steroid replacement, use of anabolic steroids, ethnic and genetic differences, sample size of the study, and use of historical or randomized untreated controls, all of which may account for the variation in final height when treated with GH.

Apart from the classic clinical phenotypic features, the diagnosis of TS should be suspected in any girl who presents with unexplained short stature even in the first 3 years of life.[15] The average age at diagnosis in a real world scenario as in our observational study was 12.7 years. Unfortunately, the diagnosis of TS is often delayed, not only because of lack of clinical expertise but also because the girl child is often neglected and brought to the attention of medical help only for evaluation of delayed puberty rather than for short stature. Adding to it is the high cost of GH therapy, and both these factors have significantly affected the use of GH therapy in this country.

We analyzed 16 TS patients attending to us over 10-year period retrospectively. Our auxological analysis demonstrates significant height gain after GH treatment. There was an increase in height from 1.26 to 1.37 m achieved with a mean duration of 25 months of GH therapy. The mean gain in height as per HSDSs when compared to the data derived from Lyon *et al*. was 0.99 and when compared to Agarwal *et al*. data was 0.63 [Table 4]. The lack of correlation of height gain with variables such as age of onset of therapy, duration of therapy, BA, and MPH may have probably been due to the small sample size.

Table 2: Distribution of Turner's syndrome characteristics

	Distribution
Karyotype	45XO - 11/16 (69%), 46XX/45XO - 2/16 (12%), structural - 3/16 (19%)
Thyroid status	Euthyrod - 11/16 (69%), Hypothyroid - 5/16 (31%)
Renal abnormalities	Horseshoe kidney - 1/16 (6.25%)
Cardiac abnormalities	Bicuspid aortic valve - 6/16 (37%), ASD - 3/16 (19%), coarctation aorta 2/16 (12%)
Mean age of presentation	12.7 years

ASD: Atrial septal defect

Table 3: Effect of growth hormone therapy on height gain and body mass index with reference to data of Lyon *et al*. and Agarwal *et al*.

n	Age GH	Duration (months)	Height start (SDS-Lyon)	Height end (SDS-Lyon)	Height change (SDS-Lyon)	HSDS (Agarwal) change	BMI start (SDS)	BMI end (SDS)	BMI SDS change
1	9	105	1.07 (−2)	1.4 (−0.38)	0.33 (1.62)	0.14	12.23 (−2.30)	18.37 (−1.02)	1.28
2	14	25	1.34 (0.2)	1.405 (0.38)	0.065 (0.18)	0.14	17.82 (−0.74)	21.28 (0.77)	1.51
3	14	12	1.405 (1.43)	1.46 (1.9)	0.055 (0.47)	0.49	16.21 (−1.74)	16.89 (−1.46)	0.28
4	15.8	26	1.26 (−2.38)	1.365 (−1.12)	0.105 (1.26)	2.21	20.16 (0.10)	24.15 (2.59)	2.49
5	10	29	1.13 (−1.4)	1.285 (0)	0.155 (1.4)	0.2	15.66 (−0.34)	16.65 (−0.97)	−0.63
6	9	30	1.05 (−2.44)	1.2 (−1)	0.15 (1.44)	0.34	10.88 (−3.38)	13.89 (−2.13)	1.25
7	15.5	7	1.31 (−1.24)	1.37 (−0.29)	0.06 (0.95)	0.92	20.4 (0.48)	18.65 (−0.82)	−1.30
8	13.3	18	1.26 (−0.95)	1.316 (−0.68)	0.056 (0.27)	−0.17	23.31 (2.88)	26.56 (4.40)	1.52
9	13	4	1.225 (−1.5)	1.255 (−1.12)	0.03 (0.38)	0.23	25.32 (4.20)	25.4 (4.12)	−0.08
10	12	18	1.32 (1)	1.44 (2.43)	0.12 (1.43)	0.82	26.4 (5.37)	25.56 (4.22)	−1.15
11	15	29	1.36 (0)	1.46 (0.73)	0.10 (0.73)	1.26	30.28 (6.65)	25.33 (3.33)	−3.32
12	14.5	9	1.38 (0.67)	1.42 (0.91)	0.04 (0.24)	0.45	17.33 (−1.11)	18.35 (−0.72)	0.39
13	11.5	20	1.285 (0.71)	1.41 (2.2)	0.125 (1.49)	0.78	21.8 (2.81)	21.13 (1.52)	−1.29
14	13.9	6	1.4 (1.4)	1.44 (1.81)	0.04 (0.41)	0.43	19.39 (0.24)	19.29 (0.12)	−0.12
15	12	18	1.24 (−0.6)	1.35 (0.64)	0.11 (1.24)	0.41	25.36 (4.72)	25.24 (4.03)	−0.69
16	11.6	45	1.12 (−2.8)	1.354 (−0.4)	0.234 (2.4)	1.39	17.54 (0.15)	18.55 (−0.64)	−0.79
Mean	12.76	25.06	1.26 (−0.62)	1.37 (0.37)	0.11 (0.99)	0.63	20.01 (1.12)	20.96 (1.08)	−0.04
SD	2.15	23.92	0.11 (1.42)	0.075 (1.20)	0.079 (0.64)	0.59	5.25 (2.95)	3.94 (2.35)	1.45

GH: Growth hormone, HSDS: Height standard deviation score, SDS: Standard deviation score, BMI: Body mass index, SD: Standard deviation

Table 4: Summary of growth parameters before and after therapy

	Before	After
Age (years)	12.7	14.8
Height (m)	1.259	1.371
HSDS Lyon	−0.619	0.376
HSDS Agarwal	−4.001	−3.374
Weight (kg)	32.6	39.6
BMI (kg/m²)	20.01	20.96
BMI SDS Agarwal	1.12	1.08

HSDS: Height standard deviation score, SDS: Standard deviation score, BMI: Body mass index

Girls with TS are thought to be prone to excessive weight, which may be a risk factor for developing diabetes and cardiovascular disease in adult life.[16,17] It is known that GH influences body composition in ways unrelated to linear growth. The mean change in BMI SDS was − 0.04, and this decrease in BMI was more apparent in individuals who had higher SDS at the start of GH treatment. Conversely, lean TS girls treated with GH had an increase in BMI suggestive of a possible beneficial effect on muscle and skeletal mass, and these observations are consistent with the observations of Corel *et al.*[18]

CONCLUSION

Our observational study in real world scenario shows that Indian girls with TS benefit from GH treatment in terms of HSDS with a possible beneficial effect on body composition and BMI. Although this study has all the limitations inherent in a retrospective study, it provokes the need for a large double-blind, placebo-controlled, prospective study to confirm these findings.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Hook EB, Warburton D. The distribution of chromosomal genotypes associated with Turner's syndrome: Livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. Hum Genet 1983;64:24-7.
2. Busschbach JJ, Rikken B, Grobbee DE, De Charro FT, Wit JM. Quality of life in short adults. Horm Res 1998;49:32-8.
3. Sybert VP, McCauley E. Turner's syndrome. N Engl J Med 2004;351:1227-38.
4. Urban MD, Lee PA, Dorst JP, Plotnick LP, Migeon CJ. Oxandrolone therapy in patients with Turner syndrome. J Pediatr 1979;94:823-7.
5. Ross JL, Long LM, Skerda M, Cassorla F, Kurtz D, Loriaux DL, *et al.* Effect of low doses of estradiol on 6-month growth rates and predicted height in patients with Turner syndrome. J Pediatr 1986;109:950-3.
6. Ranke MB. Growth hormone therapy in Turner syndrome. Analysis of long-term results. Horm Res 1995;44 Suppl 3:35-41.
7. Van den Broeck J, Massa GG, Attanasio A, Matranga A, Chaussain JL, Price DA, *et al.* Final height after long-term growth hormone treatment in Turner syndrome. European Study Group. J Pediatr 1995;127:729-35.
8. Greulich WW, Pyle SI. Radiographic Atlas of Skeletal Development as the Hand and Wrist. 2nd ed. Palo Alto, CA: Standard University Press; 1959. p. 134-81.
9. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Child 1985;60:932-5.
10. Agarwal DK, Agarwal KN, Upadhyay SK, Mittal R, Prakash R, Rai S. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. Indian Pediatr 1992;29:1203-82.
11. Mamidi RS, Kulkarni B, Singh A. Secular trends in height in different states of India in relation to socioeconomic characteristics and dietary intakes. Food Nutr Bull 2011;32:23-34.
12. Massa G, Otten BJ, de Muinck Keizer-Schrama SM, Delemarre-van de Waal HA, Jansen M, Vulsma T, *et al.* Treatment with two growth hormone regimens in girls with Turner syndrome: Final height results. Dutch Growth Hormone Working Group. Horm Res 1995;43:144-6.
13. Van den Broeck J, Massa GG, Attanasio A, Matranga A, Chaussain JL, Price DA, *et al.* Final height after long-term growth hormone treatment in Turner syndrome. European Study Group. J Pediatr 1995;127:729-35.
14. Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, *et al.* Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. J Clin Endocrinol Metab 1996;81:635-40.
15. Davenport ML, Punyasavatsut N, Stewart PW, Gunther DF, Sävendahl L, Sybert VP. Growth failure in early life: An important manifestation of Turner syndrome. Horm Res 2002;57:157-64.
16. Hanaki K, Ohzeki T, Ishitani N, Motozumi H, Matsuda-Ohtahara H, Shiraki K. Fat distribution in overweight patients with Ullrich-Turner syndrome. Am J Med Genet 1992;42:428-30.
17. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. J Clin Epidemiol 1998;51:147-58.
18. Corel LJ, Van den Broeck J, Rongen-Westerlaken C, Massa G, Wit JM. Body weight in children with Turner syndrome treated with growth hormone. Int J Obes Relat Metab Disord 1996;20:957-62.