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Research Article

Recombinant Growth hormone response in Indian girls with Turner syndrome

Introduction

Turner syndrome (TS) is characterized by short statute and ovarian dysgenesis in females with one X chromosome and partial or complete absence of the second X. It has an estimated birth prevalence of 1/2000 to 1/5000 female live births [1]. There is a global growth delay in TS characterized by slight intrauterine growth retardation, delayed growth during infancy and childhood, and lack of a pubertal growth spurt [2].

Typical stigmata include short stature, primary amenorrhoea, estrogen insufficiency and cardiovascular malformations.

Girls with TS universally have short stature (>95%), alongwith gonadal failure (>90%) and infertility (99%) [3].

Untreated these girls continue to be short and rarely achieve 150cm of adult height, barring few mosaics [4].

There have been studies that have evaluated the benefits of growth hormone in TS with significant benefit in adult height. This study has been planned to evaluate the presentation and course of Indian girls with Turners syndrome and the response to growth hormone.

Methods

A retrospective study was planned from 2010 till 2017 in Indraprastha Apollo Hospital, Delhi, in the pediatric and adolescent endocrine clinic, where all the data of girls diagnosed with Turner syndrome treated with recombinant growth hormone, was collected from the patient records.

Diagnosis was made on the basis of clinical phenotype, hormonal analysis, and confirmed by karyotypic analysis of a peripheral blood sample.

Inclusion criteria

Girls with confirmed diagnosis of TS (karyotype), with a height of <−2.5 standard deviation (SD) below the population mean.

Patient characteristics

1. **At the start of treatment:** Patient data were obtained from patient discharge records,

Height was measured to the nearest 0.1 cm (Harpenden stadiometer) and weight to the nearest 0.1 kg (Electro W-No-45). BMI (WT in kg/HT in metre^2).

Bone age was calculated using RUS score of Tanner Whitehouse 2 method.

Thyroid profile, kidney function tests, HbA1c, IGF-1, echocardiography was done at the start.

2. **At the end of treatment:** Patient parameters recorded were height, weight, BMI, tanner stage, growth velocity (cm/year).

All patients received treatment with recombinant synthetic human GH for at least 12 months, GH was administered by daily subcutaneous injections at the dose 40-50ug/kg/day.

The height SD score (HSDS) of patients was calculated based on the Turner's specific reference data described by Ranke [3,4]. The Z scores were calculated using Microsoft excel using macros. Height, weight, BMI, predicted adult height were all expressed as standard deviation scores. Independent t test and paired t test were used to compare the various pre-treatment and post-treatment data.

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Parents and most participants gave informed consent for participation in the study, which was approved by the ethical committee.

The ethical committee of the hospital approved the study. We have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals

Results

The data of 20 girls with TS who took rGH for a minimum of 12 months were included in the study. 15 girls had karyotype 45 XO, 2 cases 45 X (q10), 1 had 45, X/46,Xr(X)/46(ring chromosome), 2 were 45XX (iXq). All the girls were pre-pubertal. The data of a total of 300 girls were evaluated, who were -2.5SD below their mid parental height, who were treated with recombinant growth hormone.

Table 1 shows auxological data at presentation of these only these 20 girls who diagnosed by a karyotype were included in the study.

There was structural anomaly was seen in only 1 girl with coarctation of aorta under cardiac follow up. 3 girls had hypothyroidism, euthyroid on thyroxine at the time of initiation of treatment.

The mean age of initiation of rGH was 12.1 yr and bone age was 10.01yr. The mean duration of treatment was 13 months following with height and bone age mean at 13.2 yrs and 11.9yrs respectively.

The pre-treatment parameters are shown in table 2.

The pretreatment mean height was 123.92cm and post treatment was 130.03cm, which was statistically significant (p=0.004). The pre-treatment weight was 35.03kg and 37.67kg post treatment.

The post-treatment parameters are shown in table 3.

Rankes data for Turner girls was used to calculate Z score for pre and post treatment height and height velocity. The pretreatment height Z score was -0.91535 (+ 0.84) and post treatment was -0.28825 (+ 1.00). The pre-treatment height velocity Z score was -1.11 and post treatment was 2.79.

Table 4 comparative data of the pre and post treatment auxological data.

Discussion

An adult height deficit in TS to be around 20cm worldwide in untreated children. Mean adult height of women with Turner's syndrome ranges between 136.7 cm in Japan and 146.9 cm in Germany.

They have gonadal failure associated with delayed bone age, which can prove beneficial in treating these girls even when diagnosed at older ages. There is no apparent growth hormone deficiency in these girls, but there is a disturbed GH–IGF-I–IGFBP-3 axis and increased levels of IGFBP-3 proteolytic activity, associated with low levels of IGF-I [6,7]. This could be the reason for beneficial outcomes on treatment with recombinant growth hormone (rGH) in TS.

FDA approved recombinant growth hormone for short stature in TS in 1996, dosing at 0.33 mg/kg/wk; other approved doses are up to 0.375 or 0.469 mg/kg/wk [8]. However higher doses may be required for better height velocity, as reported in a Dutch study, the mean (SD) gains in final adult height in response to GH doses of 0.045 mg/kg/d, 0.067 mg/kg/day and 0.089 mg/kg/day were 11.9 (3.6), 15.7 (3.5) and 16.9 (5.2)cm, respectively [9].

Early age of initiation of treatment, tall parents, taller height at initiation of rGH, longer duration of treatment are usually associated with better final height outcomes [10].

There have been till date two studies from India on the use of growth hormone in Turner syndrome. One Indian study by Khadilkar reported mean age of presentation of 11.1yrs and height velocity of 6.8cm/yr in a total of 16 subjects. The second study by Danda et al reported 16 cases of Turner syndrome had a mean age 12.7yrs, the mean height SDS 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 [11,12].

The results were comparable to our study, which had a mean height velocity of 5.4cm/yr.

Table 1: Auxological data at presentation.

S.no	Auxological data	Mean value
1.	Age	12.1yrs
2.	Bone age	10.1yrs
3.	Height	123.9cm
4.	Weight	35.03kg
5.	Birth weight	2.48kg

Table 2: Pre-treatment parameters.

	N	Mean	Std. Deviation
Ht in cm	20	123.92	8.98
Wt in kg	20	35.03	11.26
BMI	20	22.50	5.94
IGF-1(ng/L)	20	121	

Table 3: Post-treatment parameters.

	N	Mean	Std. Deviation
Ht In cm	20	130.03	9.25
Wt in kg	20	37.67	11.59
BMI	20	22.03	5.69
IGF-1(ng/L)	20	134	

Table 4: Comparison of the pre and post treatment SDS of auxological data.

	Mean difference	Std. Deviation	t-value	Df	p-value
SDS Height pre – SDS Height post	-.23	0.32	-3.2	19	.004
SDS Weight pre - SDS Weight post	.091	0.19	2.0	19	.053
SDS BMI pre – SDS BMI post	.31	0.18	7.62	19	<0.001

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Despite the good result with rGH the mean final height of the girl's was130cm that is still quite less than the western data of 145cm, similar to results by Danda et al. This could be because the age of initiation of treatment in Indian studies is higher and the duration is 2yr or lesser as compared to western literature.

An RCT by Davenport in 2007 treated Turner girls between 9months to 4yrs of age with rGH and showed significant height improvements with no new or unexpected safety signals. They reported that GH could correct growth failure in infants and normalize height in toddlers with TS [13].

Our study reports very good short time height gain in Turner syndrome in Indian children. However due to financial constraints and lack of sensitization to the use of rGH in Turners syndrome in the Indian population, a long term treatment and a follow up of final height could not be assessed. There were no reported side effects in these girls, despite increasing the dose in slow responders.

Conclusion

TS should be borne in mind while evaluating any girl with short stature. However most of the girls with Turner syndrome present late, hence the early window for treatment gets delayed. Early diagnosis should be attempted in these girls, keeping in mind that early initiation could result in much improved adult height, which is very unlikely in untreated TS. The response to rGH is very good in terms of the final target height with very few side effects.

References

1. Frías JL, Davenport ML (2003) Health Supervision for Children with Turner Syndrome. Pediatrics 111: 692-702. Link: https://goo.gl/DqYcq7

2. Even L, Cohen A, Marbach N, Brand M, Kauli R, et al. (2003) Longitudinal analysis of growth over the first 3 years of life in Turner's syndrome. J Pediatr 137: 460-464. Link: https://goo.gl/BqNjWt

3. Ranke MB, Pfluger H, Rosendahl W, Stubbe P, Enders H, et al. (1983) Turner syndrome: sponta- neous growth in 150 cases and review of the literature. Eur J Pediatr 141: 81-88. Link: https://goo.gl/SSzhbo

4. Lyon AJ, Preece MA, Grant DB (1985) Growth curve for girls with Turner syndrome. Arch Dis Child 60: 932–935. Link: https://goo.gl/nXG1Fd

5. Kappelgaard AM, Laursen T (2011) The benefits of growth hormone therapy in patients with Turner syndrome, Noonan syndrome and children born small for gestational age. Growth Horm IGF Res 21: 305–313. Link: https://goo.gl/xfgA5C

6. Massa G, Heinrichs C, Verlinde S, Thomas M, Bourguignon JP et al. (2003) Belgian Study Group for Pediatric Endo- crinology, Late or delayed induced or spontaneous puberty in girls with Turner syndrome treated with growth hormone does not affect final height. J Clin Endocrinol Metab 88: 4168–4174. Link: https://goo.gl/XV5FHE

7. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W (2000) Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. KIGS International Board. Kabi International Growth Study. J Clin Endocrinol Metab 85: 4212–4218. Link: https://goo.gl/AxdkaB

8. Food and Drug Administration (2003) FDA approves humatrope for short stature. Fed Regist 68: 24003–24004. Link: https://goo.gl/EM8dsJ

9. van Pareren YK1, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, et al. (2003) Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. J Clin Endocrinol Metab 88: 1119–1125. Link: https://goo.gl/QYcQ7N

10. Stephure DK (2005) Impact of growth hormone supplementation on adult height in Turner syndrome: Results of the Canadian Ran- domized Controlled Trial. J Clin Endocrinol Metab 90: 3360–3366. Link: https://goo.gl/7h9qE6

11. Khadilkar VV, Khadilkar AV, Nandy M, Maskati GB (2006) Growth Hormone in Turner Syndrome. Indian Pediatr 43: 236-240. Link: https://goo.gl/uVyNtZ

12. Reddy Danda VS, Sreedevi P, Arun G, Rao PS (2017) Growth hormone treatment in Turner's syndrome: A real world experience. Indian J Endocr Metab 21: 378-381. Link: https://goo.gl/maoTaW

13. Davenport ML, Crowe MJ, Travers SH, Rubin K, Ross JL, et al. (2007) Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. J Clin Endocrinol Metab 92: 3406-3416. Link: https://goo.gl/qdr8et

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