Turner Syndrome: Demography, Auxology and Growth during Growth Hormone Treatment. Final and Near-final Adult Height

*ABEER ATEF ; *NORA ELSAID BADAWI ; *MAHA AMIN ; **TAREK FARID; ***ABDEL KARIM KAMEL; ASHRAF FAWZY.

**Pediatric Department, Faculty of Medicine, Cairo University.*

***National Research Centre, Cairo, Egypt.*

****Department of Biochemistry, Cairo University.*

ABSTRACT

Turner Syndrome (TS) is the most common chromosomal disorder causing short stature in females. The consequence of childhood growth failure is marked short stature in adulthood: the average height of untreated women with TS is 143cm. Treatment with human recombinant growth hormone (rhGH) in an attempt to improve height in childhood and adulthood has become a common practice. We examined the demographic and auxological features of a number of Egyptian school girls with TS and studied the growth-promoting effects of rhGH on their short stature. Twentyeight school children with TS were examined before and during treatment with rhGH. Demographic and auxological features, as well as adverse effects of the drug were important considerations. We found that rhGH had a significant growth promoting effect with very few side effects. Mean Ht SDS increased from -4.38 $\pm$ 1.03 SD to -3.2 SD $\pm$ 0.94 by the end of the third year of treatment. The difference was significant by the second year of treatment ($p<0.05$) and highly significant by the third year ($p<0.001$).

INTRODUCTION

TURNER SYNDROME (TS) is the most common chromosomal disorder causing short stature in females ***(Batch, 2000)***. Short stature is also the most consistent and main finding in these individuals. Girls with the characteristic 45, XO karyotype are smaller at birth than 46, XX girls at birth and at every point thereafter ***(Quigley et al, 2002).*** Adolescents and adults with TS may face a range of medical, fertility and psychosocial issues.

The consequence of childhood growth failure is marked short stature in adulthood: the average height of untreated women with TS is 143cm, approximately 20cm below that of average women and 20cm below genetic target height *(Betts et al, 1999).*

Treatment with human recombinant growth hormone (rhGH) in an attempt to improve height in childhood and adulthood has become a common practice in many countries ***(Johnston et al, 2001).*** In Egypt, this treatment was introduced in 1995 on a wide scale when it was provided to school health insurance to school children. Treatment with rhGH has been reported to be safe *(Chernausek et al, 2000).*

Although GH treatment for short stature in TS is an accepted treatment in many countries, which GH dosage and when to induce puberty is still an issue of debate.

This study was aimed to examine the demographic and auxological features of a number of Egyptian school girls with TS and to study the growth-promoting effects of rhGH on their short stature. In some cases, a final or near-final adult height was achieved.

Patients and Methods

Study subjects

Twenty-eight previously untreated girls with TS were observed before and after the beginning of treatment with rhGH. The diagnosis of TS was confirmed by chromosomal analysis. Inclusion criteria were as follows:

. Patients confirmed to have TS as proved by karyotyping.

. Patients not suffering from any major organ affection whose dysfunction might adversely affect growth as cardiac or renal anomalies.

. Patients with normal thyroid functions as confirmed by laboratory analysis.

. Patients who were more than 3 standard deviations (-3SD) for age and sex.

For all patients, full history taking and clinical examinations were done.

History included the following: parental consanguinity, type of delivery, whether normal or complicated and also presentation of the child,

presence of similar cases in the family, and when short stature and growth failure were noticed.

Clinical examination included a general examination for stigmata of TS and also an examination of all body systems and basal and three monthly anthropometric assessments.

Anthropometry included height (Ht), using a Harpenden stadiometer and measured twice in succession and neared to the next millimeter. Heights were measured by the same observer to minimize errors. Relation to the mean height for age and sex was calculated first in standard deviations from the mean of normal healthy girls using Tanner's standards *(Tanner and Whitehouse, 1976)* and then from the mean for girls with Turner syndrome using Ranke's standards (1999). Sitting height was also measured and from these two measurements upper to lower segments (US/LS) were derived. Midparental height and from it the target height, corrected according to child's sex was also important to assess child's deviation from normal genetic potential 1/2(mother's height + father's height – 12cm). Weight (Wt) was also measured and expressed as SDS, and body mass index (BMI) calculated. Pubertal staging was done according to Tanner's scoring system (Tanner and Whitehouse, 1976). Skeletal maturity was assessed by an X-ray of the left hand and wrist (Tanner Whitehouse no 2 method, Tanner et al, 1985). Bone age delay in years was calculated.

A measurement of growth hormone levels by dynamic testing using one or two methods (Clonidine and Insulin tolerance test) were done to assess GH status. Only those who failed the first test were subjected to the second

Study design

Biosynthetic human GH (either noditropin® or genotropin ®) injections in a total dose of 30IU/mlwk were given subcutaneously per week, divided into 6-7 doses given once at bedtime. According to the protocol, GH treatment was to be stopped when patients had grown less than 1cm in one year (final adult height).

Oestrogen was given at the end of the study period to all those who had not entered into spontaneous puberty

Subjects were assessed every 3 months anthropometrically and clinically and were questioned as to their feelings of general well being and presence or absence of side effects.

Heights in SD were compared with those of normal healthy girls (Tanner) and with girls with TS (Ranke) as were changes in estimated mature heights (EMH). Growth velocities were calculated yearly using Growth Vision (Computer) Program.

Blood samples were taken at the start of the study and yearly throughout the study period for determination of thyroid functions.

Statistical analysis

Results were expressed as mean (SD). A two-sided *P* value of 0.05 was considered significant for all tests.

Growth velocities and height SDS were estimated yearly over the study period. The differences in the studied parameters were compared using analysis of variance (ANOVA) followed by post-hoc Mann Whitney test.

The difference in Target Ht – Estimated Mature Height before and at the end of treatment was calculated.

Correlation studies were done to detect if there were any relationship between height gained and factors such as age at starting treatment and peak GH response to provocation tests.

Results

Of the 28 TS patients starting treatment with GH all completed 2 years of treatment, whereas only 26 went on to finish 3 years, 12 completed 4 years and only 1 had a five year course.

US/LS showed a mean of 1.22 revealing disproportion which is often a feature of TS.

Twenty-one showed normal GH secretion, while 6 had partial growth hormone deficiency (GHD) and only one had complete GHD.

Near-final height was available for 7 girls and a final height for 9.

Baseline data and growth during the treatment phase

Table 1 lists the baseline clinical data of the girls.

Table 1 Baseline clinical data for TS girls

Number of girls		28
Mean baseline age at presentation (yrs)		9.61+2.89
Mean baseline age at start of treatment		12.61+2.52
Mean baseline SD score for height (references healthy girls)		-4.4+1
Mean baseline SD score for height (references girls with TS)		-0.9+0.8
Mean baseline projected height (cm)		42.1+5.8
Mean Target height (cm)		157.1+3.6
Karyotypes (no.)	45X	11
	Other	17

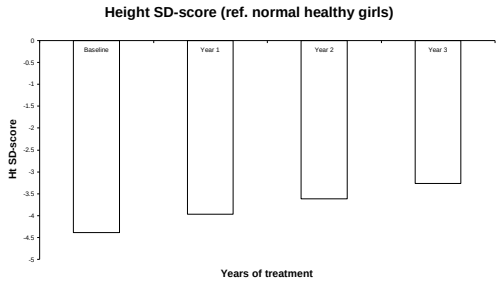

Fig. 1 Progressive height SD-score of the girls in study (no. 28) along the treatment period using references of healthy age-matched girls.

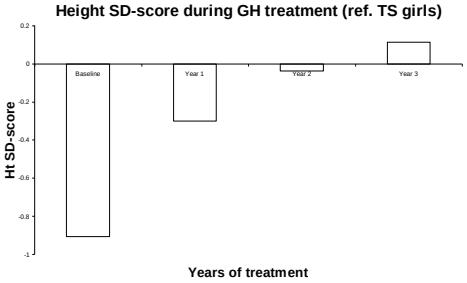

Fig. 2 Progressive height SD-scores of the girls in study (no. 28) along the treatment period using Turner references.

Mean Ht SDS according to Tanner curves for normal girls was -4.38 ± 1.03 SD at start of treatment and at the end of the 3 years was -3.2 SD ± 0.94. The difference was significant by the second year of treatment ($p<0.05$) and highly significant by the third year ($p<0.001$).

Compared to other girls with TS a significant difference was seen by the second year which increased by the third year.

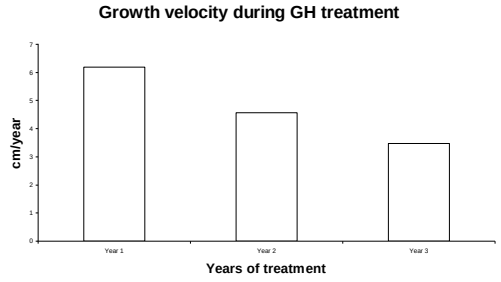

Fig. 3 Progressive mean GV in cm/year in girls (no. 28) along study period.

Mean growth velocity in the first year of the study period was 6.2cm ± 1.5 SD (GV SDS= 2.3 ± 1.5), followed by 4.6cm ± 1.6 (GV SDS= 1.1 ± 1.8) in second year and 3.5 cm ± 2 SD (GV SDS= 0.3 ± 1.7) in third year indicating an initial catchup period at start of treatment.

Target height (TH) – Estimated mature height (EMH) dropped from 14.92cm at the start of treatment to 10.77cm over 3 years and this improvement in height potential was significant ($p<0.001$).

Mean estimated mature height increased from 142cm ± 5.88 SD at start of treatment to 146.94 cm ± 6.1 SD. This difference was significant only by the end of three years of treatment.

By the end of the study period 17 of the girls (60 %) had entered into puberty. Some had entered spontaneously (N=11, 39%), while others were induced (N= 6, 21 %) using estrogen therapy.

Final and near-final adult height

Final adult height was defined as growth/year less then 1cm, whereas near-final adult height was growth between 1-2cm/year. In our group of patients, 9 patients (33%) reached their final adult height and this was a mean of 146.8cm ± 3.37 SD. Near-final adult height in 7 patients (25%) was a mean of 142.97 ± 3.93.

Linear regression analysis

Height gained along the study period correlated negatively with age at starting treatment.

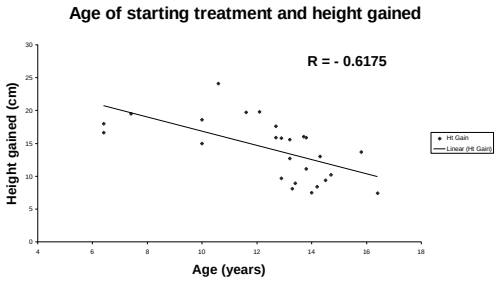

Fig. 4 The relation between height gained and age at start of treatment.

Heights gained did not correlate with peak stimulated GH levels measured using at least one growth hormone dynamic test (Clonidine).

Adverse effects of treatment

In general, therapy was well tolerated. Nineteen of the 28 (67%) suffered no adverse effects at all. The main problem that occurred was bowing of the legs in 2 of the patients (7%) which was severe enough to necessitate an operation. Minor skeletal problems were arthralgias in 2 of the girls (7 %) and leg pains in a third patient. Decreased school performance, easy fatiguability, eyelid oedema and hair loss occurred as isolated symptoms in four other girls.

Discussion:

Before the use of rhGH, the marked short stature associated with TS was a therapeutic dilemma. Henry Turner himself tried to treat these children with pituitary extract, but the results were disappointing, so he soon abandoned this form of treatment ***(Turner, 1938).*** Although the short stature is only one of the problems facing these girls, partial normalization of height may potentially improve their psychological status. Rovet et al *(1994)* reported a positive correlation between height and social competence in Turner patients. Nevertheless, GH therapy in many regimens has resulted in adult heights at least 10cm below the mean for women in the general population ***(Rosenfeld et al, 1998).*** It would appear that the residual deficit is amenable to optimization of the GH regimen: younger age at therapy initiation, longer duration of therapy and greater GH doses may improve outcome ***(Quigley et al, 2002)***. In fact, Sas et al *(1999)* found that GH treatment starting in relatively young girls with TS resulted in normalization of height during childhood as well as of adult height in most individuals.

More recently**,** it has been found that growth promotion with high-dose GH in short children without GH deficiency is influenced by the GH sensitivity, which depends on multiple gene loci involved in the functioning of the GH-IGF-I-signaling cascade as well as on the response of the epiphyseal growth plate ***(Rosenfeld and Hwa, 2004, Binder et al, 2005).*** The presence of a genetic polymorphism in the GH receptor (d3-GHR) allows a normal response to GH and normal growth in the presence of even a single copy of this gene. Turner girls who are homozygote for the d3-GHR variant of GH receptor show the highest increment in height velocity and even exceed their growth prediction, whereas those with the fl/fl genotype showed the least respone to GH treatment ***(Binder et al, 2006).***

Improvements in height SDS achieved by our patients during the study period were significant even though treatment was started late in childhood and even adolescent years and treatment period was short (only half of the patients completed 4 years of treatment). In a study by Hsu et al (2008) Turner patients who received GH for an average of 4 years at a dose of 0.33 mg/kg/week and with estrogen replacement at the age of 15.6+/-0.9 years, if indicated, reached an adult height of 150.0+/-5.1 cm, which was significantly higher than the 144.7+/-5.9 cm of their control group.

In our study, heights achieved, although significantly improved in relation to standard deviations from the mean, were suboptimal when compared with target heights even though there was a significant improvement. The reason for this is most likely due to late presentation and diagnosis of these girls. age at starting treatment. Heights gained by girls in our study correlated negatively with Final height was 146.8cm $\pm$ 3.37 SD. Near-final adult height in 7 patients (25%) was a mean of 142.97 $\pm$ 3.93.

Pubertal induction in TS should be individualized bearing in mind growth optimization and psychological factors ***(Batch, 2002).*** Spontaneous puberty occurs in 16% of women with TS and pregnancy in 4%.

Conclusion

These data indicate that rhGH has significant growth-promoting effects in girls with Turner syndrome. A minimum of 3 years appears to be necessary for a significant result. However, commencing treatment very early in childhood would be more effective for the achievement of a final height within the target centile range. Perhaps genetic studies to detect patient genotype will allow prediction of growth response to treatment and individualization of treatment accordingly.

Recombinant human GH is safe, even when given at higher levels than in the treatment of growth deficient children.

After puberty starts, little gain in height occurs so girls with TS should be identified early so that treatment may be initiated early. This way, normalization of adult height is more likely to be achieved.

References

Batch J. Turner syndrome in childhood and adolescence. Best Pract Res Clin Endocrinolo Metab 2002; 16 (3): 465 – 482.

Betts PR, Butler GE, Donaldson MDC et al. A decade of growth hormone treatment in girls with Turner syndrome in the UK. Arch Dis Child 1999; 80:221-225.

Binder G, Neuer K, Ranke MB, Wittekindt N 2005 PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. J Clin Endocrinol Metab 90:5377–5381

Binder G, Baur F, Schweizer R, Ranke MB The d3-Growth Hormone (GH) Receptor Polymorphism Is ssociated

with Increased Responsiveness to GH in Turner Syndrome and Short Small-for-Gestational-AgeChildren J Clin Endocrinol Metab, February 2006, 91(2):659–664

Chernausek SD, Attie KM, Cara JF, Rosenfeld RG Frane J, Genetech Collaborative Study Group. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. J Clin Endocrinol Metab 2000; 84: 2439-2445.

Hsu PY, Tung, YC, Tsai WY, Lee JS, Hsiao, PH. Effect of growth hormone therapy on adult height of children with Turner syndrome. J Formos Med Assoc. 2008; 107(9):704-9.

Johnston DI, Betts P, Dunger D, Barnes N et al. A Multicentre Trial of Recombinant Growth Hormone and Low Dose Oestrogen in Turner Syndrome: Near Final Height Analysis. Arch Dis Child 2001; 84: 76 – 81.

Quigley C, Crowe B, Anglin D, Chipman J and the US Turner Syndrome Study Group. Growth hormone and low dose estrogen in Turner Syndrome: results of a United States multi-centre trial

Rosenfeld RG, HwaV New molecular mechanisms of GH resistance. Eur J Endocrinol 2004 151(Suppl 1):S11–S15

to near-final height. J. Clin. Endo. Metab. 2002; 87 (5): 2033.

Rosenfeld, RG, Attie KM, Frane J, et al. Growth Hormone Therapy of Turner's Syndrome: Beneficial Effect on Adult Height. J Pediatr. 1998; 132: 319-324

Rovet J, Ireland L. Behaviour phenotype in children with Turner syndrome. J Paediatr Psychol 1994; 19:779-790.

Sas TC, Keizer-Schrama SM, Stijnen T, Jansen M et al. Normalization of Height in Girls with Turner Syndrome after Long-Term Growth Hormone Treatment: Results of a Randomized Dose-Respone Trial. J Clin Endocrin Metab 1999; 84: 4607 – 4612.

Tanner JM, Whitehouse R. Longitudinal standards for height, weight-height, height velocity and stages of puberty. Arch Dis Child 1976; 51:170-179.

Turner HH. A syndrome of infantilism, congenital webbed neck and cubitus valgus. Endocrinology 1938; 23: 566 – 574.

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