CLINICAL SCIENCE

TURNER SYNDROME: SEARCHING FOR BETTER OUTCOMES

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OBJECTIVES: To assess the results of growth hormone on the growth of girls with Turner Syndrome and identify relevant parameters to improve outcomes.
METHODS: Growth velocity and final height were studied in a historical cohort of 41 girls, regularly followed up for hormone distribution at three referral centers. The influence of oxandrolone and of estrogens on the final height was analyzed. The girls (initial chronological age=8.9±3.4years; initial bone age=7.0±3.1years) used 0.19 mg/kg/week of growth hormone for 4.0 ± 2.0 years.
RESULTS: In the first year, growth velocity increased by 71.5% in 41 girls and 103.4% in those who reached final height (11 girls). The whole group had a gain in the height SDS of 0.8 ± 0.7 ($p<0.01$) and for those who reached a final height of 1.0 ± 0.8 ($p<0.01$). Final height (143.6 ±6.3 cm) was 3.9 ± 5.3 cm higher than the predicted height, and the height gain occurred before estrogen therapy. Oxandrolone had no significant influence on height gain. The significant variables contributing to the final height were the duration of growth hormone used and its use prior to starting estrogens, the initial height SDS, and the growth velocity during the first year of treatment.
CONCLUSIONS: We concluded that the use of growth hormone significantly increased the final height, which remained lower than the target. Results point to a need for starting growth hormone use as early as possible and to maximize treatment before estrogen replacement. It has been observed that even moderate doses of growth hormone may significantly increase early growth velocity.

KEYWORDS: Growth. Growth velocity. Adult height. Growth hormone. Turner syndrome.

INTRODUCTION

The most common feature of Turner Syndrome (TS) is short stature. Without intervention, the patients attain a mean adult height approximately 20 cm below that of the control female population.

Growth failure has been ascribed to many factors[1,2] and most studies have not shown evidence of growth hormone and IGF-1 deficiencies in pre-pubertal children with TS.[3,4] Despite this, it has also been observed that treatment with recombinant growth hormone (GH) increases growth velocity (GV) in these girls.[5] TS is one of the conditions worldwide that has well-established indications for treatment with GH.

Compared with the height predicted at the beginning of treatment or to the height attained by historical control groups of patients with TS, GH supplementation was estimated to have no effect on adult height in some studies or a moderate effect in most. Factors contributing to wide variability in the estimated effects of GH supplementation on adult height include differences in treatment protocols, such as the age of initiation of GH therapy, dosing regimen, and adjuvant therapies.[6,7]

The aim of this study is to assess the effect of GH supplementation on the growth of girls with TS treated at a public program responsible for hormone distribution and to analyze relevant factors that produce the best outcomes.

SUBJECTS AND METHODS

All records of TS girls referred for GH treatment, according to the protocol established by the Department of Health from 1993 to 2004, were assessed.

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To be included in the program, their diagnosis had to be confirmed by karyotype, slow growth rate, and bone age (BA) of less than 12.5 years.[8] Moreover, the girls could not have other diseases that caused short stature.

Patients included in the study (n=41) were girls using GH for at least one year. Four girls did not have any growth promoting treatment, except for estrogens, and were followed until they reached their final height. They were used as historical controls (HC) in addition to 14 other Brazilian girls with TS described in the literature,[9] totaling 18 controls.

According to the program, the girls stopped treatment when presenting a BA above 13 years or height of 150 cm. Non-compliance or treatment interruption for more than 6 months, GV less than 3 cm per year while using GH, the occurrence of other diseases, or the use of medications that could interfere with growth were all reasons for ceasing treatment. Among the 41 girls studied, 11 reached final height.

Treatment

The patients were treated with daily subcutaneous injection of 0.5 IU/kg/week (0.17 mg/kg/week) of GH. Oxandrolone was prescribed to patients from two referral centers, with doses of 0.0625 mg/kg/day, which were interrupted before the sex steroid replacement.

Estrogen replacement was used in patients with no signs of puberty at the bone age of 13 years.[10]

METHODS

During the follow-up period, height was measured every quarter using a fixed stadiometer.

Data on height, expressed in cm and Z score (SDS), were compared to the National Center for Health Statistics (NCHS) data[11] and to the data generated by Lyon *et al*. for patients with TS.[12] GV was assessed during the first five years of treatment.

Final height (FH) was defined as the most recent reading after discontinuation of GH when GV was 1.0 cm per year or less.

The projected adult height was based on growth curves published by Lyon, assuming that without treatment, the patient would have had the same Turner standardized height at adulthood that she had at baseline.[12] The initial height SDS of each girl was then compared to the mean height of girls suffering from TS without any treatment. This method has been shown to be accurate using independent U.S. data.[13]

Target height (TH) was defined as the mean parental height – 6.5 cm.[14]

The FH was compared with the predicted final height (PFH) and with the final height of the HC; the remaining height deficit (TH – FH) was also calculated.

This study was approved by the Research Ethics Committee of the Institution. Forty-one girls were called by phone or contacted by mail. Those who were still participating in the GH program and those responding to the calls were examined and had their auxological data assessed, after having signed the informed consent.

Statistical analysis

The Student *t* test for independent samples was used to compare the means between groups. To compare means within the groups, the paired Student *t* test was used. Simple linear regression analysis was used to stratify pre-treatment and treatment variables influencing FH. Rejection of the null hypothesis was set at 5% ($p<0.05$).

RESULTS

Growth velocity

The chronological age of 41 girls at the initiation of GH therapy was 8.9 ± 3.4 years with a bone age (n=39) of 7.0 ± 3.1 years. The mean duration of GH use (n=41) was 4.0 ± 2.0 years with a mean dose of 0.19 mg/kg/week.

GV increased significantly in all girls after GH therapy. In 41 girls, pre-treatment GV increased from 3.5 ± 1.8 to 6.0 ± 1.4 cm/year during the first year (71.4%; p=0.00), which declined in subsequent years but remaining above pre-treatment GV during the first 5 years (Table 1).

Pre-treatment GV of 11 girls who completed treatment was 2.9 ± 1.8 cm/year, increasing to 5.9 ± 1.5 cm/year (p=0.00) in the first year. GV decreased in the subsequent years but remained greater than that prior to treatment. Catch-up growth occurred in the first two years of treatment compared to the Lyon curve. Height SDS gain (0.4 ± 1.1 SD) coincided with a significant GV increase in the first two years of treatment as compared to the pre-treatment GV (p=0.00) (Figure 1).

Table 1 - Growth velocity in TS girls before and after treatment with GH

	Pre-GH	Year 1 post-GH	Year 2 post-GH	Year 3 post-GH	Year 4 post-GH	Year 5 post-GH
GV (cm/y) (n=41)	3.5 ± 1.8	6.0 ± 1.4	5.2 ± 1.3	5.2 ± 1.3	4.6 ± 1.8	4.3 ± 1.4
GV (cm/y) (n=11)	2.9 ± 1.8	5.9 ± 1.5	5.7 ± 1.0	4.8 ± 1.4	4.0 ± 1.8	3.0 ± 2.3

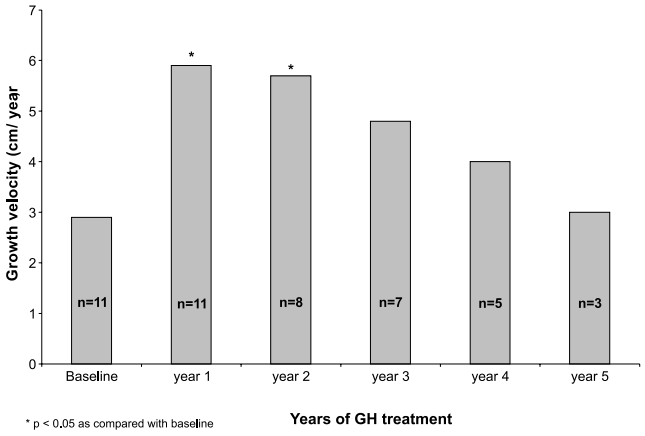

Figure 1 - Mean GV increase in TS girls after rhGH compared to initial GV

Out of 41 girls, 24 used associated oxandrolone and 17 used GH exclusively. Table 2 shows that despite a higher pre-treatment GV of the girls receiving oxandrolone, the increase was similar in both groups in the three years following GH treatment. Therefore, no benefits of GV were observed with the use of oxandrolone. There was no difference in age at baseline between the two groups as well as in GH dose.

According to the Lyon curve, 24 girls using oxandrolone, and 17 girls that did not use it grew similarly (p=0.88).

Final Height

The characteristics of the 11 TS girls who reached FH are depicted in table 3. Mean duration of GH use was 3.6 ± 1.7 years and the follow-up time from GH cessation to FH was 2.5 ± 1.7 years. Mean GH dose in the first year of treatment was 0.15 mg/kg/week, reaching a peak of 0.18 mg/kg/week during the first 5 years.

Mean FH was 143.6 ± 6.3 cm, corresponding to -3.1 ± 0.9 SD (NCHS) or 0.5 ± 1.0 SD (Lyon). FH surpassed the PFH described by Lyon by 3.9 ± 5.3 cm, which is a significant gain in height (p=0.03).

There was a significant increase in height SDS compared to baseline according to NCHS (0.5 ± 0.7 SD, p=0.04) and Lyon (1.0 ± 0.8 SD, p=0.00) standards. After GH discontinuation, there was no significant increase in the height of the patients followed up, until they reached FH.

Final height surpassed TH, minus 20 cm, which is in agreement with the international pattern [15] by 6.7 ± 6.3 cm, resulting in a significant gain in height (p=0.01). The difference between final height (139.9 ± 7.0 cm) and target height (TH = 154.4 ± 5.5) of the Brazilian Historical Controls was 15.5cm. There was no significant increase in FH of the girls studied compared to their TH minus 15.5cm (p=0.27).

The height deficit of 11 girls who reached FH was 13.3

Table 2 - Growth velocity in TS girls before and after treatment with GH alone or associated with oxandrolone (Mean ± SD)

	Pre-GH (n=37)	Year 1 post-GH (n=41)	Year 2 post-GH (n=35)	Year 3 post-GH (n=22)
Oxa group + GH (cm/y)	4.1 ± 2.5 (n=21)	6.3 ± 1.9 (n=24)	5.3 ± 1.2 (n=24)	5.2 ± 1.4 (n=18)
GH group (cm/y)	2.7 ± 3.0 (n=16)	5.7 ± 1.9 (n=17)	5.1 ± 1.6 (n=11)	5.4 ± 1.0 (n=4)
* p	0.02	0.2	0.7	0.8

**t* test comparing the two groups

Table 3 - Characteristics of 11 TS patients who reached final height (Mean ± SD)

	Pre-treatment	Data at the end of GH	Post treatment	Height gain	p *
CA years	11.5 ±2.2	15.2 ± 1.3	17.7 ± 1.8		
BA years	9.1 ± 2.1 (n=10)		13.9 ± 1.0 (n=11)		
ΔBA/ΔCA years			1.08		
Height cm	122.4 ± 11	140.1 ± 7.4	143.6 ± 6.3		0.00
Weight SD	-1.7 ± 1.1		-1.6 ± 1.3		0.84
Pre-treatment GV	2.9 ± 1.8				
TH cm	156.8 ± 5.1				
PFH cm (Lyon)	139.6 ± 6.6			3.9± 5.3	0.03
Height SD(NCHS)	-3.6 ± 0.8	-3.2 ± 0.9	-3.1 ± 0.9		0.04
Height SD (Lyon)	-0.4± 0.9	0.7 ± 1.1	0.5 ± 1.0		0.00

* Paired *t* test comparing final to baseline data

± 6.3 cm relative to their target height.

Estrogen replacement in 11 girls was started at the age of 14.6 ± 1.4 years, after 3.0 ± 2.1 years using GH. While using GH before starting estrogens, a significant height increase relative to the Lyon chart was observed (0.9 ± 0.6 SD, p=0.00), which was not maintained after initiating estrogen replacement until final height was reached (0.1 ± 0.5 SD, p=0.66), as shown in figure 2.

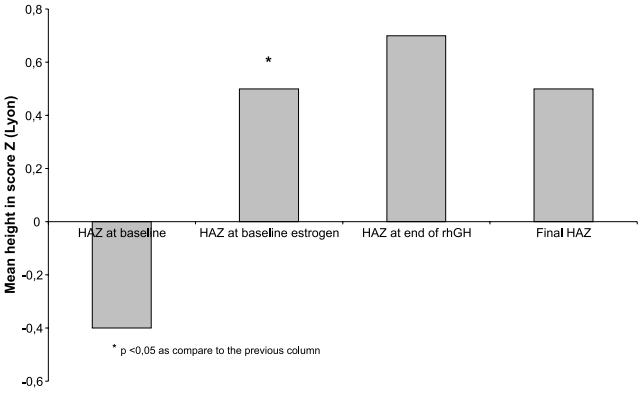

Figure 2 - Influence of estrogen replacement in the growth of the 11 girls with TS during rhGH use

In the simple linear regression analysis, the factors associated with an increase in final height relative to initial height were duration of GH use ($p<0.05$), duration of GH use prior to starting estrogens ($p<0.05$), the initial height SDS ($p<0.05$), and GV in the first year ($p<0.05$).

The factors associated with reaching greater final height SDS were the baseline height SDS ($p<0.05$) and the parental target height ($p<0.05$). That is, the smaller the height deficit and the greater the parental target height when the treatment was started, the better the outcome for FH.

DISCUSSION

Reports on the FH of girls with TS treated with GH are highly variable. The mean increase by 6.0 cm in final height relative to the predicted height (ranging from -0.2 to 16.9 cm) and the mean FH of 150.3 cm[16] still raises concerns about the clinical relevance of the treatment. Among the problems involving comparative assessments are the considerable differences among study protocols regarding sample size, doses, age at the start of the treatment, and the associated use of estrogens and oxandrolone. The first clinical randomized trial carried out in Canada showed a FH of 147.5 ± 6.5 cm (TH= 160.7 ± 6.2) with a mean height gain of 7.2 cm. The authors concluded that GH supplementation increased the adult height of girls with TS and that the benefits of GH supplementation needs to be balanced against the cost of therapy and the need for daily subcutaneous injections over a period of many years.[17] A statistically significant increase in height during GH use was observed in the present study. Despite this, the FH attained by the girls can be considered insufficient when compared to that of the general population. The girls reached a final height of 143.6 ± 6.3 cm, which represented a mean increase of 4 cm relative to the PFH. We should bear in mind that lower doses were prescribed for these girls compared to most other reports. American FDA approved doses are 0.054 mg/kg/d (0.38 mg /kg/week).[18] In the Canadian study, girls were given 0.30 mg/kg/week.[17]

There is evidence that the increase in FH in girls with TS depends on age at start of treatment,[19] duration of GH use[6,10,19] and the duration of its use prior to estrogen replacement,[10,15,20,21] which are tightly interdependent factors. An association between FH and height at the start of the treatment was seen,[19] as well as with TH.[15,19,22]

The GH dose may also influence FH.[6,10,19] Studies conducted on patients with either GH deficiency or TS demonstrated that the response to GH treatment is dependent on the dose and on the frequency of GH administration.[6,22] Poor final outcomes are frequently attributed to the low initial dose of GH used. However, in the present study, a significant improvement in GV was observed in response to GH and the increase in GV in the first year of treatment was similar to that reported in studies employing higher initial doses,[24,25] followed further by a rapid decrease, which has also been reported.[23,24-26] In 11 girls who reached FH, GV accelerated 103.4% in the first year and 75.8% in the second year of treatment as compared to the pre-treatment GV.

Despite the gradual decline, GV during the first five years of treatment was still higher than the pre-treatment GV. However, the increase in GV was significant only in the first two years due to the decline in the response to GH. This effect was also reported in studies from the Netherlands[24,25] that demonstrated an increase in GV by 100% during the first year of treatment with GH at a dose of 0.9 IU/kg/week relative to pre-treatment GV. A similar increase was observed in the present study using a lower GH dose. However, such an increase in GV was not maintained during subsequent years of treatment, which has also been reported in the literature.[23,26,27] This decline was also observed in children with GH deficiency and could be overridden by increasing the GH dose 2- to 3-fold.[23,28] Some studies suggested that the GV drop in girls with TS could also be compensated by the progressive increase in GH doses, reducing the final loss.[25,29] Thus, it seems that these girls could benefit from an increased dose as GV declines. Taken together, this raises the question of whether this should be the best way to administer treatment.

Takano[30] studied pre-pubertal girls with TS using two regimens of GH doses (0.5 and 1.0 IU/kg/week) and verified

a significant increase in GV in the first 2 years of treatment in the group receiving the higher dose. However, no significant differences in GV after the third year and especially, on the final height between the two groups after 6 years of GH use were observed.[5] This suggests that the use of high, fixed doses does not prevent the decline in GV and therefore would not be recommended.

In a recently published consensus of the TS study group, it was assumed that doses substantially higher than those approved by the FDA produce a relatively small gain in final height.[18]

On the other hand, there is no significant difference between induced and spontaneous puberty with regard to final height,[31] but data regarding the appropriate time to induce puberty with estrogens are conflicting.[20,21,32-34] Height gain was observed prior to estrogens and not after they were started in our studied population. Chernausek[13] showed that TS girls who started estrogen replacement at 12 years of age had reduced height gain compared to those starting it at the age of 15 years. However, the number of years of GH treatment before estrogens was the single most important factor for predicting the response to treatment, as also shown by other authors.[10,20] Van Pareren[21] and Reiter[20] reported that girls with TS who received GH for at least 4 years before starting estrogens reached FH within the usual range, even with the onset of puberty at a physiological age.

It is known that at a bone age of 9 years, the difference in mean height between TS girls and normal girls is about 16 cm, a deficit found almost throughout adult life. The international literature shows that untreated TS girls reached a final height 20 cm shorter than their target height.[15,19,22] Thus, from puberty on, there is little additional height loss compared to normal girls, despite the absence of the pubertal growth spurt. It is reasonable to think that if the treatment with GH was started before this age, the height deficit could be reduced prior to the induction of puberty, and the estrogen replacement could start at an appropriate time.

Some studies suggest that final height can be normalized when treatment begins earlier and when the doses of GH are higher and titrated.[29,32,33,35]

We demonstrated that the duration, in years of GH use, the duration of use before estrogens were started, the initial height SDS, and the first year GV were the variables associated with an increase in height SDS. Catch-up growth occurred in the first two years of treatment and prior to estrogen replacement.

The results reported here point to the need for starting treatment with GH as early as possible in order to prevent further height deterioration and to maximize treatment prior to estrogen replacement that could take place during a physiological age. This study showed that the use of GH, even in modest doses, may promote a significant increase in the initial GV. Further evaluations should be conducted in order to determine if increasing the dose as GV decreases may be beneficial to the patients. Insufficient GV responses early in the treatment may justify the use of higher initial doses. Further studies are still needed to clarify these issues.

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