

Experience With 68 Girls With Turner's Syndrome and Evaluation of Final Height in 26 Patients Treated With Growth Hormone in Combination or Without Oxandrolone

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Short stature is a common feature in Turner's syndrome; (TS) final height in untreated patients is on average 20cm below the population mean for adult women. When recombinant growth hormone (GH) became available, supraphysiologic GH doses with or without oxandrolone (OX) were administered in order to improve growth in patients with TS in several studies

Objective: The objective of this study was to find out whether moderate doses of growth hormone in combination with oxandrolone and late initiation of puberty could improve adult height even in TS patients with late diagnosis.

Materials and Methods: In this study the data on 68 patients with TS will be reported. Thirty-three patients with chronological age 17 years or above did not receive treatment. Thirty-five patients with TS were randomly assigned to receive either GH alone (0.375 mg/kg/week) by daily S.C injections (Group GH, n = 23) or in combination with OX 6 mg/kg/day P.O (group GH + OX, n = 12). Mean age at the onset of treatment was 10.7 years (GH) and 10.3 years (GH+OX), mean projected adult height (PAH) was 142.1 cm (GH) and 141.5 cm (GH+ ox).

Puberty was induced at a mean age of 14.5 years.

Results: There was a marked difference in group GH \pm OX cumulative growth during 4.3 years of therapy in comparison with untreated TS patients. Twenty-six patients are now near or at final height: Group GH (n=17), mean final height was 148.7 cm (PAH 142.1 cm, gain 6.6 cm); group GH+ OX (n = 9), 151.9 cm (PAH, 141.5 cm, gain 9.4 cm). In the untreated group (n = 33), mean final height was 139.1 cm. Cumulative growth was more significant in GH plus OX than GH alone treated subjects (P<0.001).

Conclusion: The diagnosis of TS is often delayed in our country and this defers the timely and appropriate treatment of short stature. Our results are in keeping with studies demonstrating moderate doses of GH plus OX and late induction of puberty are able to improve final height even in patients with TS, treated relatively late.

Key Words: Turner's syndrome, Growth hormone therapy, Oxandrolone, Final height

Introduction

Turner's syndrome (TS) affects approximately 1 out of every 2000-2500 female live births corresponding to approximately 1.5 million affected women worldwide.¹⁻³

TS is the result of complete chromosome monosomy in about 40-50% of patients,

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while the rest show a multitude of chromosomal abnormalities including absence of one X chromosome or mosaicism.^{4,5} The phenotype is undoubtedly female, and is associated with characteristic clinical features, the most frequent being short stature and hypergonadotropic hypogonadism due to gonadal dysgenesis.^{1,2,6,7}

While classic hormonal deficiency is likely not a cause of growth failure¹, partial growth hormone insensitivity could be involved, as suggested by the finding of reduced free IGF-I (Insulin like growth factor I).⁸

The median adult height of untreated women with TS is 143 cm, 20 cm (8in) below that of the general female population.^{7,9,12}

Today, most patients with TS are treated with GH to improve adult height.^{1,6,13-20}

Those starting GH earlier will experience a greater increase in height. If at the time of initiation of therapy, height is significantly below 5% and the child is 9 to 12 years, anabolic steroids such as oxandrolone can be used in combination with GH to hasten the growth spurt. If however bone age advances excessively, oxandrolone therapy should be discontinued.⁴

Virilization including facial hair and clitorimegaly are side effects of anabolic steroids and should be monitored.^{4,21,22}

To date no study with respect the effect of GH with or without Oxandrolone (OX) on final height in patients with TS has been conducted in Iran.

This study was designed to investigate whether moderate doses of GH in combination with oxandrolone and late initiation of puberty could improve final height even in patients with TS treated relatively late; the main clinical features, age at diagnosis and karyo type finding were also determined.

Materials and Methods

68 patients with TS who were followed in the pediatric endocrine clinic at Imam Khomeini Hospital, Tehran will be reported.

The age range of study participants varied between 3-19 years (mean; 13.9 ± 4.2)

All patients were examined by a pediatric endocrinologist. An extensive health history was taken and a systemic physical examination was performed.

Data were collected on age, height, weight and parental height. Height was measured at base line and subsequently every 2 months using a wall mounted stadiometer. Auxological calculations were performed according to the Turner specific growth chart available on the website for TS Society of the United States.²³ All measurements were obtained in cm and transformed into standard deviation scores (SDS).

Bone age was determined prior to and once a year after initiation of GH therapy by skilled investigators using the method of Greulich and pyle.

Target height was estimated from mid parental height as recommended by Tanner. Projected adult height (PAH) was calculated according to the method of Lyon et al²⁴ applying pretreatment SDS (for chronological age) for adult height SDS (standards of Ranke et al).²⁵ Of 68 TS patients, 33 subjects did not receive stimulated growth therapy because of late diagnosis (with a chronologic age 17 years or above)

Thirty-five patients were enrolled in this study. They were randomly assigned to receive either GH (0.375 mg/ week) injected daily S.C (Group GH) or the same dose of GH plus OX %6 mg/kg/day orally (group GH + OX) Thus, finally there were three groups of patients: untreated group (n=33), group GH (n = 23) and group GH + OX (n =12).

The mean age of the patients at the onset of treatment was approximately 10.5 years.

The mean duration of stimulated growth therapy was $4/3 \pm 2.6$ years.

Estrogen treatment for induction of puberty was initiated at least four years after growth stimulated therapy.

During the first year of therapy ethinyl estradiol was given in a daily dosage of 5 µg for the first 6 months and 10 µg for the second half year. Height, weight, tanner staging monitored every 2 months after initiation of estrogen therapy. Most girls experienced tanner 3 breast development within 1 year.

Table 1. Characteristics of 68 Turner's patients at the start of study (All data are presented as mean \pm one standard deviation)

	GH	GH+ OX	Untreated
n	23	12	33
CA (yr)	10.7 \pm 2.4	10.3 \pm 2.6	17.8 \pm 1.2
BA (yr)	8.3 \pm 1.6	8.5 \pm 1.7	15.9 \pm 1.8
Height SDS	-4.1 \pm 1.8	-3.9 \pm 1.9	-4.3 \pm 1.4
Target height (cm)	158.9 \pm 4.3	159.2 \pm 4	160.3 \pm 3.9
Height velocity (cm/yr)	3.8 \pm 1	3.6 \pm 1.1	< 0.5

Results are means \pm SD; CA = chronologic age; OX = oxandrolone; BA = bone age; SDS = standard deviation score

The dose of estrogen was gradually increased to adult dose (mean age 16.8 \pm 1.1 years), at this estrogen dose (or at a lower dose if vaginal spotting occurred or if breasts reached tanner stage 4) cyclic therapy was initiated. This consisted of a combination of estrogen for the first 25 days of every month and medroxyprogesterone (5 mg) from 14-25.

Chromosomal findings and clinical data were very similar in both GH and GH + oxandrolone groups: 45 XO in 57% / 56% /, 45 XO /46 XX or other mosaics in 38%/ 37% and structural abnormalities in 5%/ 7%, mean chronologic age; 10.7 \pm 2/4, and 10.3 \pm 2.6 years, bone age; 8.3 \pm 1.6 and 8.5 \pm 1.7 years, height SDS; -4.1 \pm 1.8 and -3.9 \pm 1.9, target height; 158.9 \pm 4.3 and 159.2 \pm 4 cm, projected adult height (PAH); 142.1 \pm 2.9 and 141.5 \pm 1.8cm, height velocity; 3.8 \pm 1 and 3.6 \pm 1.1cm/year, respectively.

Chromosomal findings and clinical data in untreated group were: 45 XO in 54%, 45 XO/46XX or other mosaics in 40.4% and structural abnormalities 5.6%, mean chronologic age; 17.8 \pm 1.2 years, bone age; 15.9 \pm 1.8 years, height SDS; -4.3 \pm 1.4, target height; 160.3 \pm 3.9 cm and height velocity below 0.5 cm/ year, respectively table1 shows the patients in this group were near or at final height at the start of study, and these patients were accepted as control group (untreated group).

Statistical analysis was performed using SPSS version 9.4 (SPSS, Inc. Chicago, IL/for windows. Differences between groups was

compared by non parametric Mann- Whitney U- test and student t test. Values of P<0.05 were considered to be statistically significant.

Results

Among 68 TS patients, 35 (56%) subjects had complete X chromosome monosomy (45 X) while the rest showed a multitude of chromosomal abnormalities, including partial absence of one X chromosome or mosaicism. Short stature (100%) and delayed puberty (78%) were the most common complaints. At present, among 35 patients who had received growth stimulated therapy, 26 subjects (17 in GH group and 9 in GH + OX group) and 33 untreated TS patients are near or at final height.

These patients reached chronological age at 17 years or above and their height velocity had fallen to or below 0.5 cm/year. Individual baseline characteristics and last recorded data at final height in GH and GH + oxandrolone treated groups are shown in Table 2.

Mean final height (FH) was 148.7 \pm 5.1cm in group GH, 151.9 \pm 5.2cm in group GH + oxandrolone and 139.1 \pm 6.1 cm in untreated group. The difference in FH between treated and untreated groups was statistically significant (P< 0.001)

Treatment results were more significant in GH plus oxandrolone treated patients than in GH alone treated subjects (p<0.001). The mean gain over baseline projected adult height was 6.6 cm and 9.4 cm in the GH and GH + oxandrolone group respectively.

Table 2. Characteristics of 26 patients with Turner's syndrome at baseline and at final height (All data are presented as mean \pm one standard deviation)

	<i>GH</i>	<i>GH+OX</i>
n	17	9
pretreatment		
CA (yr)	10.7 \pm 2.4	10.3 \pm 2.6
BA (yr)	8.3 \pm 1.6	8.5 \pm 1.7
Height SDS	-4.1 \pm 1.8	-3.9 \pm 1.9
Height velocity (cm/r)	3.8 \pm 1	3.6 \pm 1.1
Target height	158.9 \pm 4.3	159.2 \pm 4
PAH (cm)	142.1 \pm 2.9	141.5 \pm 1.8
At the end of treatment		
CA (yr)	17.8 \pm 1.2	17.5 \pm 1.3
BA (yr)	15.4 \pm 1.1	14.9 \pm 1.3
Height SDS	-2.2 \pm 1.1	-1.8 \pm 0.9
FH (cm)	148.7 \pm 5.1	151.9 \pm 5.2
PAH	142.1 \pm 2.9	141.5 \pm 1.8
Over PAH (cm)	6.6 \pm 3.2	9.4 \pm 2.1

GH = Growth hormone ; OX= Oxandrolone ;
CA= chronological age; BA = bone age ; PAH =
projected adult height; FH = final height

There was no significant bone age acceleration in patients receiving either GH alone or in combination with OX.

Discussion

A cardinal clinical feature of TS is linear growth failure resulting in extreme short stature. Growth hormone alone or in combination with anabolic steroids, seems to improve the growth rate in Turner's syndrome.

The reported gain in final height following therapy was between 3-16 cm in various studies.¹³⁻²⁰

In keeping with other reports¹³⁻²⁰ in this study, there was a marked difference between stimulated growth and growth without therapy, the best results being obtained with a combination of GH and OX.

In this investigation, we treated our patients with North American study protocol but in that study height increment was more impressive than in our study. The most marked height increment being found in the Sas and colleagues study¹⁵ using a maximum GH dose of approximately 0.63mg/kg/week for

4.8 estrogen free GH treatment years beginning at mean age 8.1 years, resulting in a gain of 16cm over the modified Lyon projection.

Our results are rather conservative, and should be regarded as an underestimate of true final height since some of the patients are still growing and only the patients who had been older at initiation of treatment have already achieved adult height.

Some treatment studies archived favorable results while others have not. Several factors (age of patients at beginning of treatment, GH dose, duration of GH treatment, concurrent oxandrolone therapy, age at the start of estrogen substitutive therapy) may be involved in discrepancies in the reported gain in final height in various studies.

There is a significant relationship between midparental height or target height and adult height.^{1,2,20} There has been much controversy about the appropriate age to induce puberty by estrogen supplements.^{4,20,21,22,26} Meanwhile, it has become quite clear that even low estrogen doses advance skeletal maturation, thus impairing treatment outcome. Therefore late introduction of estrogens preferably at an age of 14 to 15 years (in our study mean age at puberty initiation was 14.5 years), is recommended if the already achieved height is not yet satisfactory and in girls who began GH therapy at a late age.

It must be noticed that pubertal bone mineralization could also be delayed by late start of puberty but there is no risk of osteoporosis in these patients with late puberty, since GH administration has been shown to increase bone mineral density.²⁰

Multiple liner regression analysis revealed that the addition of OX to GH clearly improves the outcome.^{1,3,4} In this study and in other reports, the highest increment in final height was obtained with GH plus OX.^{13-15, 20,22} This combination therapy may offer advantages: patients grow faster during the first years, they achieve a greater height at adolescence, thereafter earlier induction of puberty maybe possible and the treatment period may be shorter.¹³

With OX, lower doses of GH are effective.²⁰ A low dose of OX should be employed but not until bone age 9 years, to avoid undue bone age, acceleration.^{1,3,4,20}

A crucial point in every growth-stimulating therapy is the effect on bone age development. In addition, with the relatively high dose of OX, some signs of virilization may be observed.²¹⁻²² In keeping with other reports,^{14-16,20} in this study there was no consistent bone age acceleration or virilization due to GH and low dose OX therapy. The chro-

mosomal pattern was quite similar in the two treatment groups. In this study in agreement with stahnke et al report²⁰ no relationship between the karyotype and growth of patients has been found.

From a clinical point of view, the average age at diagnosis is often late in our TS patients. We highly recommend seeking the diagnosis in short girls at any age and initiating therapy at a younger age.

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