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# Response to growth hormone therapy in patients with Turner syndrome

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***Summary***

**Aim:** Short stature, a common feature of Turner syndrome (TS), may be treated effectively by recombinant human growth hormone (rhGH). In this study we aimed to evaluate response to rhGH in the first three years of therapy.

**Material and Method:** Medical records of 46 girls with TS treated with rhGH were evaluated retrospectively. Karyotypes, age at admission to the hospital, age at the beginning of rhGH therapy, the height of the mother and father were recorded. Data including, height and weight, growth velocity, dose of rhGH therapy, bone age and predicted height of subjects at the beginning of rhGH therapy and one, two and three years after rhGH therapy were recorded. The difference between target height z-score and height z-score is defined as delta z-score.

**Results:** Age at admission to hospital, age at the beginning of rhGH therapy and target height were 10.2±3.8 years, 11.54±3.03 years and 157.0±6.0 cm, respectively. The height z-score at the beginning of rhGH therapy and one, two and three years after rhGH therapy was -3.76±1.00, -3.37± 1.01, -2.99±0.97, -2.82±1.01, respectively and the growth velocity was 3.24±1.05, 6.53±1.52, 5.77±1.53, 5.19±1.25 cm/per year respectively. The growth velocity in the first year and the chronological and bone age at the beginning of therapy were correlated negatively with delta Z-score and the father's height and positively with growth hormone dose. Bivariate correlation analyzes revealed that the most important factors affecting the growth velocity in the first year were the chronologic age at the beginning of therapy and growth hormone dose.

**Conclusions:** Major factors affecting response to rhGH therapy were age, rhGH dose and delta z-score. As the major predictor of the growth velocity is age at the beginning of therapy, these girls must be treated with rhGH as soon as possible after diagnosis.. *(Turk Arch Ped 2013; 48: 294-298)*

**Key words:** Growth hormone, Turner syndrome, treatment

## Introduction

Turner syndrome (TS) occurs as a result of partial or complete absence of one X chromosome and short stature is one of the important characteristics of this syndrome (1). Untreated patients are 20-21 cm shorter compared to normal adults in their own populations (2). Although it was thought that growth hormone (GH) therapy would not be beneficial in TS patients in the past, it has been shown that therapeutical GH doses above the physiological dose can improve growth velocity (3,4,5). However, the effect of GH therapy on the final height is substantially variable and individual differences are observed in TS patient (6). It is thought that several clinical and genetic factors lead to this variability. Braz et al. (7) reported that polymorphisms related with GH receptor and/or IGFBP3 gene might affect the response to GH therapy negatively in TS patients. Ghrowth hormone dose, age at the beginning of treatment, body weight standard deviation score, the difference between the target height Z-score and present height Z-score

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(delta Z-score), use of oxandralone and weekly number of injections were found to be the clinical factors which might affect the growth velocity. Mathematical models have been developed to predict growth velocity using these variables (8). In this study, we aimed to investigate the response to GH treatment and the clinical factors which might affect the growth velocity in children with TS in our country.

## Material and Method

The medical records of 46 TS patients who presented to our hospital from the Marmara region (predominantly İstanbul) and received GH treatment were examined retrospectively. The karyotype, age at the time of presentation, age at the beginning of GH treatment, maternal and paternal heights and height, weight and body mass index (BMI), yearly growth velocity, GH hormone, bone age and predicted height values were recorded.

The target height was calculated using the following formula: (paternal height +maternal height-13)/2. In addition, the target height Z-score was calculated using the formula (target height-160.0)/6.6 based on the national growht curves (9). The difference between target height Z-score and present height Z-score was expressed as delta Z-score. The predicted adult height was calculated using the method recommended by Bayley and Pinneau (10). The BMI Z-scores of the patients were calculated using the method recommended by Cole (11). The results of GH stimulation tests performed using clonidine and L-Dopa were recorded additionally.

All statistical analyses were done using SPSS 15.0 package program. The relation between yearly growth velocity and other variables was evaluated using Pearson's correlation test. Multiple regression analysis was performed to evaluate the factors which might affect growth velocity. In comparison of the growth variables in the beginning of treatment and one, two and three years after treatment, "one way ANOVA" test (posthoc Tukey tests) was used.

## Results

The karyotype distribution of our patients is shown in Table 1. The most common genotype was found to be 45XO. The demographic analysis results of our patients are shown in Table 2. Our results showed that the age at the time of the onset of GH treatment was meanly 1.34 years after the diagnosis. Another finding was the fact that the predicted height at the beginning of treatment was similar to the final height (Table 2). The initial dose was 0.25 mg/kg/week in patients with an old diagnosis, while a dose of 0.36 mg/kg/week has been used recently.

A significant improvement was observed in the height Z-score with treatment and the difference between the target height Z-score and height Z-score (delta Z-score) regressed from 3.22±1.38 to 2.06±1.30 at the end of the three-year treatment (Table 3). The best response to growth hormone was obtained in the first year of treatment and it was found that the growth velocity increased approximately two-fold compared to the pre-treatment period (Figure 1). It was observed that estrogen replacement treatment was started at a mean age of 14.75±1.46 years. At the time when the files were examined, it was observed that 29/46 patients had started to use estrogen and 24 of these 29 patients had been using estrogen for one year and longer. No acceleration in the bone age was observed until estrogen replacement trreatment was started. It was found that the bone age increased by a mean time of 1.3±0.4 years in the first year with estrogen treatment. It was found that the patients who reached their final heights were treated with GH for a mean time of 2.7±1.2 years (the shortest 0.8- the longest 4.25 years) and GH treatment was ended a mean time of 1.63±0.95 years after estrogen was started in these patients.

The growth velocity in the first year and the chronological and bone age at the beginning of therapy were correlated negatively with delta Z-score (the difference between target height Z-score and present height Z-score) and the father's height and positively with growth hormone dose (Table 4). In the second year of treatment, the growth velocity was only correlated with the chronological age and bone age. In the second year of treatment, the growth velocity showed

**Table 1. Karyotype distribution**

| | n | % |
|---|---|---|
| 45 XO | 19 | 41.3 |
| 46 i(Xq) | 5 | 10.9 |
| 45XO/46XX | 3 | 6.4 |
| 45XO/46 i(Xq) | 9 | 19.6 |
| 46Xr(X) | 5 | 10.9 |
| Other | 5 | 10.9 |
| Total | 46 | 100 |

**Table 2. Demographic properties of the patients**

| | |
|---|---|
| Age at the time of presentation to hospital (years) | 10.2±3.8 |
| Height of the mother (cm) | 157.1±7.3 |
| Height of the father (cm) | 169.9±6.4 |
| Target height (cm) | 157.0±6.0 |
| Target height Z-score | -0.53±1.03 |
| Age at onset of GH treatment (years) | 11.54±3.03 |
| Adult height predicted before treatment (cm) | 144.23±5.43 |
| Final height (cm) (n=14) | 144.97±6.05 |
| Final height Z-score | -2.28±1.02 |

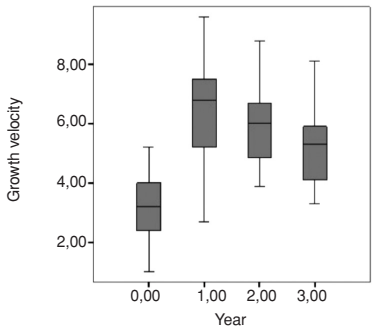


**Figure 1. Growth velocity by years (cm/years)**

a negative correlation with the bone age and a positive correlation with the growth velocity found in the first year. It was observed that karyotype and GH stimulation test results had no effect on the growth velocity.

## Discussion

One of the important findings of this study is the fact that the mean age at the time of diagnosis in our patients was 10.2 years and treatment could be started as late as a mean time of 1.34 years after diagnosis. However, this study showed that early treatment provided positive contribution to growth velocity. Previously, Linglart et al. (12) showed that early treatment with GH provided a normal

**Table 3. Growth variables by years**

| | At baseline | At the end of the first year | At the end of the second year | At the end of the third year | p |
|---|---|---|---|---|---|
| Height (cm) | 122.8±12.1 | 128.9±11.2 | 134.8±9.9 | 137.5±8.6 | |
| Height Z-score | -3.76±1.00 | -3.37± 1.01 | -2.99±0.97 | -2.82±1.01 | <0.001 |
| Delta Z-score* | 3.22±1.38 | 2.90±1.40 | 2.40±1.30 | 2.06±1.30 | 0.045 |
| Predicted height (cm)* | 144.2±5.4 | 145.8±5.1 | 147.2±5.1 | 148.1±6.1 | 0.023 |
| Weight | 29.8±9.3 | 33.9±10.2 | 39.2±10.7 | 43.0±11.3 | |
| BMI (kg/m$^2$) | 19.36±3.16 | 19.96±3.58 | 21.24±3.89 | 22.47±4.06 | |
| BMI z-score*** | 0.69±0.51 | 0.74±0.44 | 0.76±0.23 | 0.86±0.63 | <0.001 |
| One age (years) | 9.3±2.5 | 10.3±2.0 | 11.6±2.0 | 12.2±2.1 | |
| Growth velocity (cm)** | 3.24±1.05 | 6.53±1.52 | 5.77±1.53 | 5.19±1.25 | <0.001 |
| GH dose (mg/kg/day) | | 0.036±0.006 | 0.036±0.005 | 0.034±0.005 | 0.542 |

Delta z score= (target height z-score)-(height z-score), BMI: Body mass index, GH: growth hormone

*As a result of Posthoc test, a statistical difference was found between the baseline and the third year results

** As a result of Posthoc test, a statistical difference was found between the baseline and the first, second and third year results.

*** As a result of Posthoc test, the BMI z-scores at the end of the first and second years were significantly higher compared to the baseline and the BMI z-score at the end of the third year was significnatly higher compared to the first and second years.

**Table 4. Correlation coefficient and p values of variables which might be related with the first, second and third year growth velocities**

| | First year | | Second year | | Third year | |
|---|---|---|---|---|---|---|
| | r | p | r | p | r | p |
| Age at the beginning of GH treatment | -0.566 | <0.001 | -0.627 | <0.001 | -0.160 | 0.454 |
| Delta Z-score | -0.491 | <0.001 | -0.148 | 0.389 | 0.163 | 0.447 |
| GH dose | 0.470 | <0.001 | 0.297 | 0.078 | -0.534 | 0.009 |
| Bone age before treatment | -0.539 | <0.001 | -0.514 | <0.001 | -0.162 | 0.451 |
| Height of the mother | -0.173 | 0.266 | -0.165 | 0.337 | 0.133 | 0.536 |
| Height of the father | -0.330 | 0.031 | -0.087 | 0.614 | -0.265 | 0.211 |
| Peak response to GH stimulation (clonidine) | -0.001 | 0.994 | -0.132 | 0.442 | 0.287 | 0.174 |
| Growth velocity before treatment | 0.148 | 0.331 | -0.090 | 0.601 | 0.434 | 0.034 |
| Growth velocity in the first year of treatment | | | 0.314 | 0.062 | -0.221 | 0.299 |
| Growth velocity in the second year of treatment | | | | | 0.173 | 0.418 |

GH: growth hormone

growth in terms of height in many TS patients. Similarly, Rose et al. (13) emphasized the finding that 62.3% of TS patients could achieve normal height Z-score values with GH treatment which lasted for longer than 3 years and thus the importance of early treatment and continuance of treatment. Although patients are diagnosed at younger ages in developed countries, some patients in some countries cannot be diagnosed until the adulthood (14,15). In our patient group, one of the reasons of delayed presentation and diagnosis may be the low socioeconomical level of the group to which we offer service.

Although GH treatment has been used for more than 40 years in TS patients, the criteria to be used in evaluation of response to treatment have been defined recently (16). Bakker et al. (16) recommended evaluation of growth velocity at the end of the first year and dose adjustment if the response was insufficient. However, this approach may lead to loss of time in countries where the diagnosis is delayed including our country. Therefore, we think that mathematical samples which can predict the response to GH treatment may be beneficial in directing treatment.

The second important finding in our patient group was improvement in height Z-score with treatment and positive correlation of this improvement with GH dose. In a retrospective study, Van Pareren et al. (17) showed that the patients who received high dose GH treatment achieved a better final height compared to the patients who received low dose GH treatment. Different doses have been used in treatment in different countries. Increasing the treatment dose from 0.36 mg/kg/week to 0,46mg/kg /week was approved by FDA (18). In Japan, a dose of 0.35 mg/kg/week was started to be used since 1999 (18). In our center, the therapeutic dose was 0.25 mg/kg/week in previous years, while a dose of 0.36 mg/kg/week has been used in recent years. This allowed us to evaluate the relation between the dose and growth velocity. In some studies, it was observed that higher doses like 0.63 mg/kg/week were more effective, but insulin like growth factor-1 (IGF-1) levels in some patients who used this dose reached values close to the levels found in patients with acromegaly (5). The authors reported that IGF-1 values which stayed high for long periods might have potential cancerogenic effect hypothetically and therefore recommended avoidance of very high doses of GH which lead to high IGF-1 levels (1,19). All this information suggests that higher doses with monitoring of IGF-1 levels might be beneficial in some patients who do not give sufficient response to treatment.

Ranke et al. (8) reported that treatment should be planned individually because of high cost of treatment and variable response to treatment. Different mathematical samples were recommended in predicting response to treatment (8,20). Ranke et al. (8) reported that questioning should be done in cases where there are big differences between the prediction made using these samples and treatment response obtained. However, some investigators found that these samples in which only clinical variables were used were not sufficient and biochemical variables including IGF-1 levels could improve prediction values of treatment response (21). In addition, polymorphism studies performed on GH receptor suggest that molecular genetic examinations may also be included in prediction samples in the future (7,21).

Conclusively, the age at the beginning of treatment, GH dose and delta Z-score were important factors which affected the growth velocity in the first year. Especially, when the relation of the age at the beginning of treatment with growth velocity was evaluated, the necessity of starting treatment as soon as possible emerged. As a result of this study, it was observed that Turkish children with TS had a similar response to GH treatment compared to developed countries and therefore mathematical prediction samples developed previously could also be used in our population.

## Conflict of interest: None declared.

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