Effect of Growth Hormone Therapy on Adult Height of Children with Turner Syndrome

Ping-Yi Hsu, Yi-Ching Tung, Wen-Yu Tsai,* Jing-Sheng Lee, Pei-Hung Hsiao

Background/Purpose: Short stature is a common manifestation of Turner syndrome. The purpose of this study was to evaluate the effect of growth hormone (GH) therapy alone on the adult height of children with Turner syndrome.

Methods: From 1987 to 2006, 21 Turner syndrome patients who had been treated with GH for > 2 years and had reached adult height were enrolled in the study. The dosage of GH was 0.33 mg/kg/week. Estrogen replacement therapy was prescribed at the age of 15.6 ± 0.9 years, if indicated. The patients had been followed-up until they reached their adult height. During the same period, 28 Turner syndrome patients who were not treated with growth-promoting agents were enrolled for comparison. Mann-Whitney U test and Wilcoxon signed rank test were used for comparison.

Results: Twenty-one patients in the study group started GH therapy at the age of 11.5 ± 1.8 years. The duration of GH therapy was 4.0 ± 1.5 years. The growth rate before treatment was 3.8 ± 0.7 cm/year, which increased to 7.1 ± 1.4, 5.4 ± 1.4 and 4.7 ± 0.9 cm/year during the first 3 years of GH therapy, respectively. Patients who received GH reached an adult height of 150.0 ± 5.1 cm, which was significantly higher than the 144.7 ± 5.9 cm of the control group (p < 0.05). The adult height of the study group was 6.3 ± 3.3 cm taller than their projected adult height upon enrolment. No major adverse events were detected during GH therapy.

Conclusion: GH alone is safe and effective for the promotion of growth in children with Turner syndrome in Taiwan. [J Formos Med Assoc 2008;107(9):704–709]

Key Words: body height, growth hormone, Turner syndrome

Turner syndrome was first described by Henry Turner in 1938 as a syndrome of infantilism, congenital webbed neck and cubitus valgus caused by the complete or partial absence of X chromosome.1,2 Short stature is a common manifestation in these children, which may impair their quality of life.1,3–5

Initially, Turner et al reported that growth hormone (GH) could not improve the adult height of their patients,1 but several subsequent studies have since demonstrated the effectiveness of GH therapy in Turner syndrome patients over the past 20 years.6–19 There is considerable variation in the treatment protocols for GH therapy of Turner syndrome patients in the literature.6,7,9,11,14–19 One study has reported that the combination of GH with fluoxymesterone can improve the adult height of children with Turner syndrome in Taiwan.20 However, an effect of GH alone on the adult height of these patients in Taiwan is lacking. Therefore, the present study was conducted to investigate the effect of GH therapy alone on the adult height of Turner syndrome patients.
Methods

The medical records of Turner syndrome patients who visited the National Taiwan University Hospital between 1987 and 2006 were reviewed. Diagnosis was made on the basis of their clinical phenotype and confirmed by karyotype analysis of peripheral blood leukocytes. Twenty-one patients who received GH therapy for >2 years and reached an adult height were enrolled. For comparison, 28 Turner syndrome patients who were never treated with growth-promoting drugs were enrolled as controls.

Study group

Twenty-one patients who had not been treated with growth-promoting agents were enrolled for GH therapy. They did not have any clinical evidence of severe cardiovascular diseases, renal diseases, scoliosis or other major systemic diseases. Chromosome analysis demonstrated a 45,X karyotype in eight patients, mosaicism in 12 patients, and structural abnormalities of the X chromosome in one patient. After baseline observation for >6 months, GH was prescribed at a dose of 0.33 mg/kg/week.

At the start of treatment, the chronological age was 11.5 ± 1.8 years and bone age was 10.0 ± 1.9 years, according to Greulich and Pyle’s standards.21 Body height was −3.2 ± 0.8 standard deviations (SD) below the mean height of normal Taiwanese girls of the same age. The mean growth rate was 3.8 ± 0.7 cm/year. GH therapy was continued until the patients grew <4 cm/year, or when they and their parents were satisfied with the height achieved. The duration of GH treatment was 4.0 ± 1.5 years.

Only one patient had spontaneous puberty and menstruation, and hormone replacement therapy was prescribed for the other 20 patients. The average age at the start of estrogen therapy was 15.6 ± 0.9 years. Administration of conjugated estrogens was initiated at 0.3 mg/day, which was increased to 0.625 mg/day, and given cyclically with the addition of progesterone after 1 year.

The patients have been regularly followed-up at our pediatric endocrine clinic at least once every 3 months. During the period of GH therapy, body height and weight, signs of puberty, complete blood count, fasting blood glucose level, and plasma HbA1c levels were checked once every 3 months. Bone age, thyroid autoantibodies, and thyroid function were checked once every 6 months.

Control group

Twenty-eight patients who had never been treated with growth-promoting agents were enrolled as the control group. Chromosome study showed a 45,X karyotype in seven patients, mosaicism in 16 patients, and structural abnormalities of the X chromosome in five patients. Twenty-three patients had not been treated with GH because their parents refused treatment, and they were followed-up until their adult height was reached. The other five patients were too old to receive GH therapy paid for by health insurance on their first visit to our hospital. Estrogen replacement therapy was indicated in 20 of the 28 patients. Their age at the start of therapy was 16.4 ± 2.4 years. The treatment protocol was the same as that of the study group.

Auxological parameters

Patient height was obtained by direct measurement on a wall-mounted Harpenden stadiometer, while the growth rate was calculated using measurements for 6–12 months. The target height (TH) was calculated using the following equation:

\[(\text{mother’s height} + \text{father’s height} - 13)/2 \text{ cm}\]

Adult height was considered when the annual growth rate was <2 cm and the bone age was >15 years. The projected adult height (PAH) of the patients was estimated according to the data described by Lyon et al.3 In the control group, there was a good correlation between height standard deviation scores (SDS) on the first visit of the patient and those of their observed adult height (r = 0.81). Therefore, Turner-specific reference data described by Lyon et al were used to estimate PAH in this study.
Statistical analysis
Numerical data in this study were presented as mean ± SD. Mann-Whitney U test and Wilcoxon signed rank test were used for comparison of numerical data and \( p < 0.05 \) was considered statistically significant. Correlations between adult height SDS and variables were analyzed by Spearman’s rank test.

Results
In the control group, there was no statistically significant difference in the PAH or observed adult height between those receiving estrogen therapy and those with spontaneous puberty. Neither the study nor control group had a statistically significant difference in PAH or observed adult height between patients with mosaicism and those with non-mosaicism. Therefore, these data were grouped together.

As shown in the Table, there were no statistically significant differences in age, height, Turner height SDS, PAH and TH between the group receiving GH therapy and the control group upon enrolment.

There was a marked increase in growth rate, from 3.8 ± 0.7 to 7.1 ± 1.4 cm/year, during the first year of GH therapy (Figure 1). The change in growth rate was not as dramatic in the following years, but there were statistically significant increases in growth rate during the first 3 years of GH therapy, as compared with the baseline growth rate.

There was no statistically significant difference between PAH and the observed adult height in the control group at the end of the study (Table).

![Figure 1. Growth rate during growth hormone therapy in Turner syndrome. Numbers in parentheses denote number of patients. *\( p < 0.05 \).](image)

**Table.** Auxological data of patients with Turner syndrome

<table>
<thead>
<tr>
<th></th>
<th>GH</th>
<th>Control</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>11.5 ± 1.8</td>
<td>12.9 ± 4.0</td>
<td>0.154</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>125.2 ± 7.8</td>
<td>129.7 ± 13.4</td>
<td>0.088</td>
</tr>
<tr>
<td>Height SDS</td>
<td>−3.2 ± 0.8</td>
<td>−2.9 ± 1.1</td>
<td>0.129</td>
</tr>
<tr>
<td>Turner height SDS†</td>
<td>0.1 ± 0.7</td>
<td>0.4 ± 0.9</td>
<td>0.146</td>
</tr>
<tr>
<td>PAH (cm)†</td>
<td>143.8 ± 4.0</td>
<td>145.7 ± 5.6</td>
<td>0.157</td>
</tr>
<tr>
<td>TH (cm)</td>
<td>156.4 ± 3.0</td>
<td>155.5 ± 4.7</td>
<td>0.363</td>
</tr>
<tr>
<td>Age at estrogen therapy (yr)</td>
<td>15.6 ± 0.9</td>
<td>16.4 ± 2.4</td>
<td>0.223</td>
</tr>
<tr>
<td><strong>Data at end of study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last age (yr)</td>
<td>20.6 ± 3.1</td>
<td>20.6 ± 4.2</td>
<td>0.840</td>
</tr>
<tr>
<td>Adult height (cm)</td>
<td>150.1 ± 5.1</td>
<td>144.7 ± 5.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Adult height SDS</td>
<td>−1.7 ± 0.9</td>
<td>−2.7 ± 1.1</td>
<td>0.004</td>
</tr>
<tr>
<td>( \Delta ) Adult height – PAH (cm)</td>
<td>6.3 ± 3.3</td>
<td>−1.0 ± 3.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( \Delta ) Adult height – TH (cm)</td>
<td>−6.3 ± 4.5</td>
<td>−10.9 ± 6.7</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Baseline age was the age at the start of growth hormone therapy for the study group and the age at the first visit for the control group; †estimated using the method of Lyon et al. SDS = standard deviation scores; PAH = projected adult height; TH = target height.
On the other hand, the adult height of the study group, who were treated with GH for 4.0 ± 1.5 years, was significantly higher than the PAH and adult height of the control group. The difference between adult height and TH was -6.3 ± 4.5 cm in the study group and -10.9 ± 6.7 cm in the control group, which was statistically significant. Although the average adult height of Turner syndrome patients treated with GH was 150.0 ± 5.1 cm, which was -1.7 ± 0.9 SD below the mean adult height of normal Taiwanese women, 57% achieved an adult height above the third percentile for normal Taiwanese adult women.

The increment in height relative to PAH in patients with Turner syndrome is shown in Figure 2. The height increment in patients treated with GH was significantly greater than the change in height of patients without GH therapy. However, two patients in the study group had no obvious height gain after 2 years of GH therapy.

When covariance was analyzed with adult height as the end point, a significant positive correlation was observed with TH \( (r=0.467) \), baseline height SDS \( (r=0.689) \), baseline growth rate \( (r=0.525) \), and growth rate during the first year of therapy \( (r=0.440) \). However, no significant correlation was demonstrated with age at the start of GH therapy and duration of therapy.

GH therapy was well tolerated. There were no episodes of leukemia, neoplasm, diabetes mellitus, hypothyroidism, slipped capital femoral epiphysis, or benign intracranial hypertension during the study period.

### Discussion

The mean observed adult height of the control group \((144.7 ± 5.9 \text{ cm})\) was similar to their PAH \((145.7 ± 5.6 \text{ cm})\), estimated by the method of Lyon et al upon study entry,\(^3\) which suggests that the method is applicable for estimating the adult height of Taiwanese patients with Turner syndrome. The observed adult height of the control group was higher than that previously reported for Turner syndrome in Taiwan.\(^{20,22}\) The fact that only those with severe manifestations of Turner syndrome tended to seek medical help in previous times may partially explain such a discrepancy.

The growth rate was markedly increased during the first year of GH therapy. Such an increment was not as remarkable during the second year of therapy, as previously reported.\(^{23}\) However, there was still a statistically significant increase in growth rate above baseline in the first 3 years of GH therapy. Based on the differences between annual growth rate after GH therapy and baseline growth rate, it was estimated that up to 77% of the total increase in adult height above PAH was obtained during the first 3 years of GH therapy.

The observed adult height of the study group was 150.1 ± 5.1 cm, which was 6.3 ± 3.3 cm taller than their PAH, and 95% had an adult height greater than their PAH. The adult height was also better than that of the control group, which was comparable to that reported in the literature.\(^6\)–\(^{19}\) Although the adult height of the study group was shorter than their TH, 57% were taller than the third percentile for normal adult height of Taiwanese women.
It has been reported that the adult height of Taiwanese children with Turner syndrome can be improved by treatment with a combination of GH and fluoxymesterone.\(^\text{20}\) The TH and observed adult height in our study group were similar to those reported by Shu,\(^\text{20}\) which implies that GH therapy alone is as effective as combination therapy in Taiwanese children with Turner syndrome. On the other hand, GH therapy alone avoids the androgenic side effects of fluoxymesterone in combination therapy.\(^\text{20}\) However, two of 21 patients (9.5%) treated with GH had their observed adult height similar to their PAH. Such a phenomenon has also been noted previously,\(^\text{7,15,24,25}\) which suggests that individual variations in response to GH therapy do exist in Taiwanese patients with Turner syndrome.

The adult height of children with Turner syndrome treated with GH was related to their TH, baseline height SDS, baseline growth rate, and growth rate during the first year of therapy as previously reported.\(^\text{10,19,20}\) Although there was no notable correlation between the observed adult height and age at onset or duration of GH therapy, early initiation of GH therapy in patients with Turner syndrome is advisable, so that puberty can be induced at the appropriate age during adolescence.\(^\text{8,11,17}\)

The fact that no obvious major side effects were observed in patients receiving GH therapy during the study period confirms its safety.

Our study has all the limitations inherent in a retrospective study. A large double-blind, placebo-controlled, prospective study is required to confirm our findings. Our study showed that GH therapy alone is safe and effective for improving the adult height of patients with Turner syndrome in Taiwan.

References


