

Clinical Investigation

Adult Heights of 258 Girls with Turner Syndrome on Low Dose of Growth Hormone Therapy in Japan

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Abstract. Growth hormone (GH) therapy was approved in 1999 for only GH-deficient Turner syndrome (TS) in Japan. It was subsequently approved for all cases of TS regardless of GH secretory status since 1999. The dose of GH is 1.0 u (0.35 mg)/kg/wk at present, but it was 0.5 u (0.175 mg)/kg/wk before 1999. The adult height in patients with TS on the dose of 0.5 u/kg/wk was studied from the report on of Foundation for Growth Science in 2000. GH therapy was registered for 920 cases, and 258 cases reached adult height. The mean adult height was 145.7 cm. The adult height in patients with TS without GH therapy was reported to be 138 cm in Japan. Thus, the height gain by GH treatment was 7.7 cm. The mean age at the start of GH therapy was 12.0 yr old. The mean duration of GH therapy was 5.6 yr. The mean age at the start of estrogen therapy was 17.0 yr old. Patients in Japan were older at the start of GH and estrogen therapy than in the US and Europe at that time. The adult height and gain of height SD were not correlated with age at the start GH therapy in this study. This may be the result of the older age at the start of GH therapy and the low dose of the GH therapy. Patients are beginning to start GH therapy at a much earlier age and the dose has been doubled in Japan. We expect that the recent data concerning adult height in the patients with TS after GH therapy will improve better than this report.

Key words: Turner syndrome, growth hormone, estrogen, adult height

Introduction

Growth hormone (GH) therapy has been approved for Turner syndrome (TS) in many countries. It used to only be approved for GH-

deficient TS in Japan. The dose of GH was 0.5 u (0.175 mg)/kg/wk. GH therapy was approved for all cases of TS regardless of GH secretory status since 1999. The dose of GH was doubled to 1.0 u (0.35 mg)/kg/wk at that time. The historical data concerning adult height with the low dose of GH therapy needs to be published. This study reviewed the data from the report of the Foundation for Growth Science in 2000. The adult heights of patients with TS and age at the start of estrogen therapy were studied.

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Subjects and Methods

Nine hundred and twenty cases of TS with GH therapy were registered with the Foundation for Growth Science by 1999. Questionnaires were sent to each doctor who registered these cases of TS. Answers were received from 607 cases (65.9%). Two hundred and fifty-eight cases reached adult height among them. The definition of adult height depended on the doctor.

The indication for GH therapy was that the peak GH level was less than 10 ng/ml in more than two provocative tests for GH. GH therapy was indicated when the peak GH level was higher than 10 ng/ml in the provocative tests, and if the peak GH level was less than 10 ng/ml in more than two other provocative tests. The dose of GH was 0.5 u/kg/wk.

Results

Adult height after GH therapy was 145.7 ± 5.2 cm. The adult height in patients with TS without GH therapy was previously reported to be 138 cm in Japan (1). Therefore, the height gain by GH treatment was 7.7 cm. The mean adult height for Japanese girls was 158 cm. The adult height in patients with TS with GH therapy was still 12.3 cm less than the mean Japanese adult height (Fig. 1). The age at the start of GH therapy was 12.0 ± 2.5 yr old. The age at the termination of GH therapy was 17.7 ± 1.9 yr old. The duration of GH therapy was 5.6 ± 2.4 yr. The age at the start of estrogen therapy was 17.0 ± 2.4 yr old. The age at the start of Kaufman therapy was 18.3 ± 1.8 yr old.

There was no difference in adult height between cases with spontaneous breast development and cases without spontaneous breast development (Table 1). Adult height was lower in the cases with spontaneous vaginal bleeding than in the cases without spontaneous vaginal bleeding (Table 1).

Adult height was compared between two groups of cases based on mean age at the start

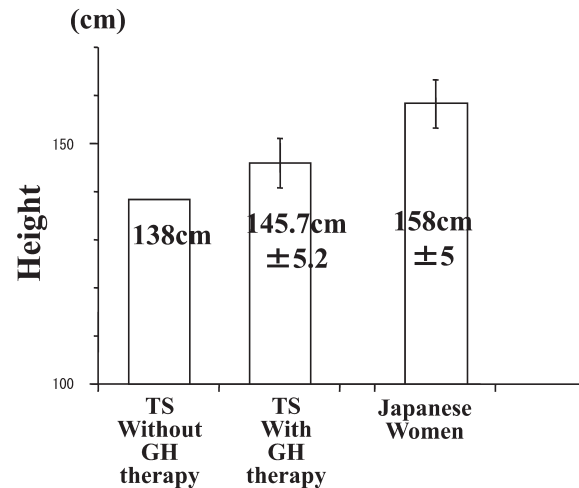


Fig. 1 Adult height in Japanese patients with TS with and without GH therapy and mean adult height of Japanese women. The vertical bars show the SD score.

of GH therapy, a younger group (less than 12.0 yr old) and an older group (12.0 yr old or older. Table 2). The younger age group did not show a higher adult height. The age at the start of estrogen therapy was also compared between these two groups, and the data showed that the age was the same in the two groups (Table 2).

According to the peak values of a stimulation test for GH, the adult heights of the cases with more than 10 ng/ml were the same as those that received less than 10 ng/ml (Table 3).

The target heights calculated from the heights of the parents correlated with the adult heights (Fig. 2). The target height was calculated as $(\text{height of father} + \text{height of mother})/2 - 6.5$ cm (girl) + 2 cm (secular trend).

The height SD score before GH therapy was -3.6 SD for the standard of Japanese girls and -2.3 SD after GH therapy. The gain of the SD score was $+1.3$ SD (Fig. 3).

The ages at the start of GH therapy were not correlated with the change of the SD score for the Japanese girls (Fig. 4).

Table 1 Adult height in patients with TS according to pubertal condition

Pubertal condition	Adult height
Cases with spontaneous breast development (n: 40)	144.1 ± 5.6 cm
Cases without spontaneous breast development (n: 73)	145.1 ± 5.2 cm
Cases with spontaneous vaginal bleeding (n: 25)	141.9 ± 4.6 cm
Cases without spontaneous vaginal bleeding (n: 87)	145.5 ± 5.3 cm

Table 2 Adult height and the age at the start of estrogen in two groups based on age at the start of GH therapy

Age at the start of GH therapy	Adult height
Before 12.0 yr old (n: 102)	144.2 ± 5.4 cm
After 12.0 yr old (n: 137)	146.8 ± 4.9 cm

Age at the start of GH	Age at the start of estrogen
Before 12.0 yr old (n: 58)	17.0 ± 2.4 yr old
After 12.0 yr old (n: 81)	17.1 ± 2.3 yr old

Table 3 Adult height in two groups based on peak GH level

Peak GH level at the stimulating test	Adult height
Less than 10 ng/ml (n: 145)	145.5 ± 5.2 cm
More than 10 ng/ml (n: 110)	146.0 ± 5.3 cm

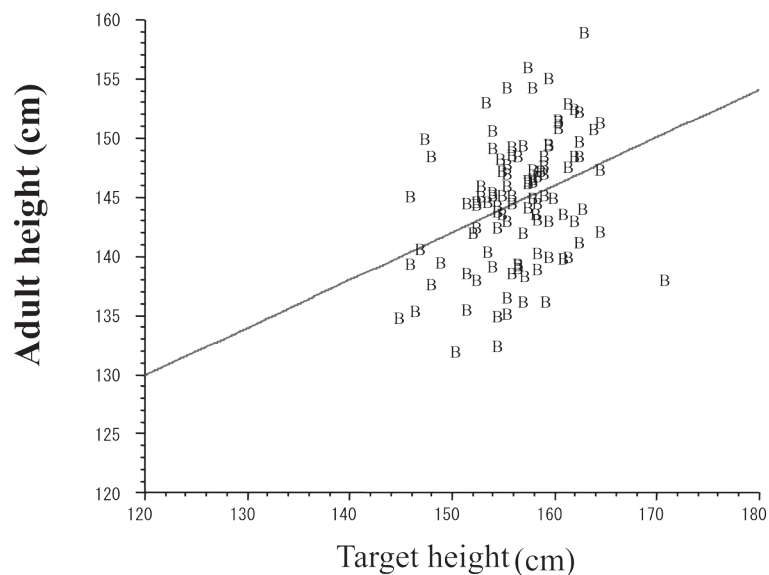


Fig. 2 Correlation between the target height and adult height.

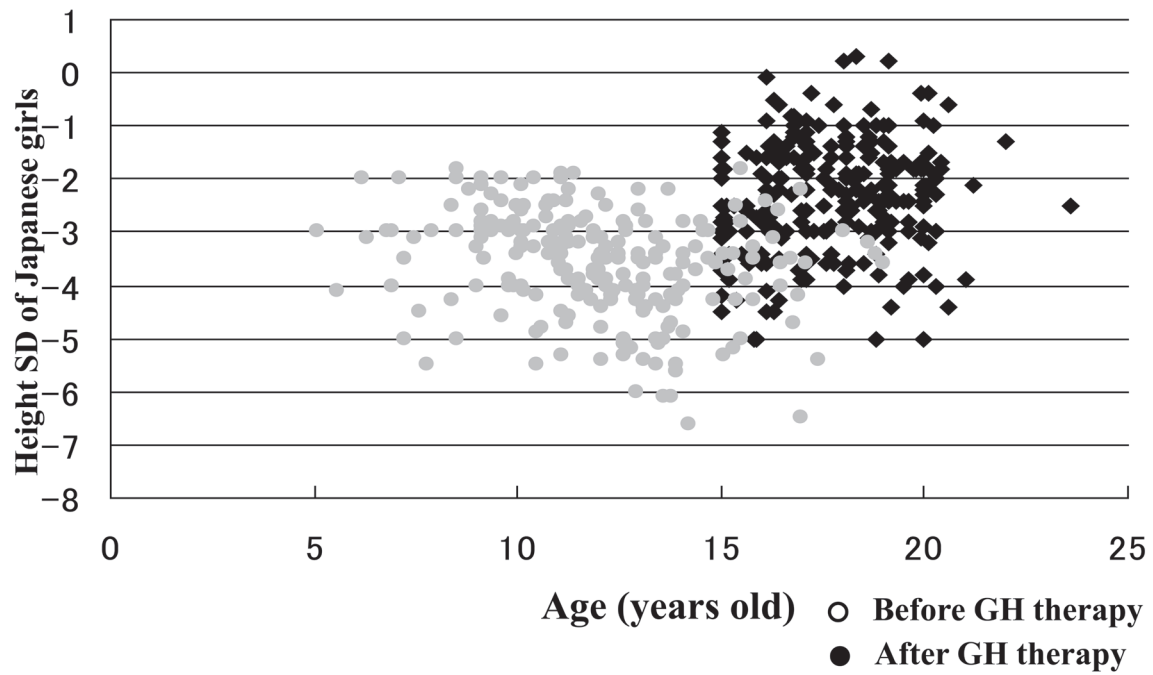


Fig. 3 Effect of GH therapy on the height SD score of Japanese girls.

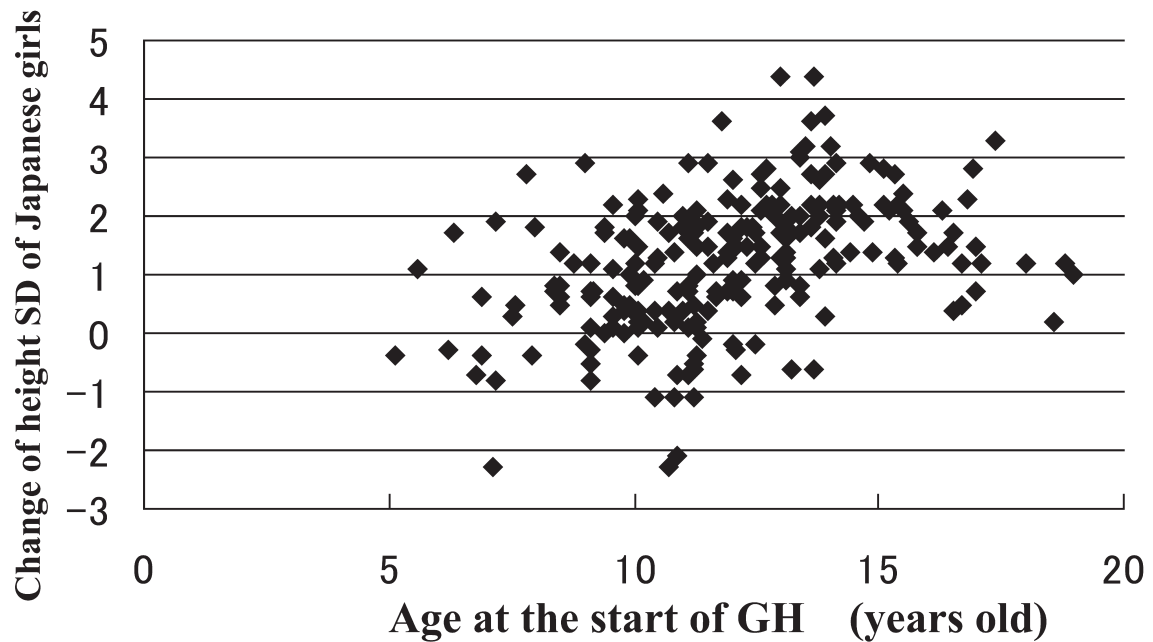


Fig. 4 Correlation between age at the start of GH therapy and gain of height SD score of Japanese girls.

Discussion

Historical data concerning adult height after GH therapy with a dose of 0.5 u/kg/wk were examined in the present study. The data were studied from the report of the Foundation for Growth Science in 2000.

The mean adult height was 145.7 cm. The height gain with GH treatment was 7.7 cm based on the mean height of Japanese TS patients without GH therapy. However, the above height is still 12.3 cm shorter than the mean adult height of Japanese girls. Many studies have reported the adult height after GH therapy in Europe and the United States (2–5). These data showed that adult height increased by 5.2–8.4 cm the adult height without GH therapy. The standard doses of GH were 0.7–1.125 u/kg/wk in these reports. Carel *et al.* and Sas *et al.* reported the dose dependent effect of GH therapy using much higher doses (4, 5). Carel *et al.* reported that the adult height in the lower dose group (0.9 u/kg/wk) was 148.3 cm, 5.2 cm higher than the projected adult height, and that it was 155.3 cm, 10.6 cm higher than the projected adult height, in the higher dose group (2.1 u/kg/wk) (4). Sas *et al.* reported that adult height was 158.8 cm at a dose of 0.95 u/kg/wk, 161.0 cm at a dose of 1.5 u/kg/wk and 162.3 cm at a dose of 2.0 u/kg/wk (5). Adult height can be normalized using a high dose of GH. The dose of GH in Japan used to be 0.5 u/kg/wk, and the dose was doubled in 1999. We expect that the adult heights of patients with TS after GH therapy with a dose of 1.0 u/kg/wk will improve more.

Adult height and the gain of height SD were not correlated with age at the start of GH therapy in this study. Quigley *et al.* reported that younger subjects had a greater increase in height SD score (6). The mean age at the start of GH therapy in their study was 9.7 yr old. This age was younger than our age of 12 yr old. The doses of GH in their study were 0.77 u/kg/wk and 1.0 u/kg/wk. These doses were more than our dose of 0.5 u/kg/wk. The fact that there was no correlation of

adult height and gain of height SD with the age at the start of GH therapy in our study may be the results of the late age at the start of GH and the low dose of the GH therapy. The age at the start of GH therapy is getting much younger, and the dose of GH has been doubled in Japan. We expect that the adult height in patients with TS after GH therapy will improve more.

The mean age at the start of estrogen therapy was 17.0 yr old. This age was older than in Europe and the United States (6, 7). The delay of estrogen therapy in Japan may be also the result of the late age at the start of GH therapy. When GH therapy was started at a late age, the gain in height was insufficient, and the start of estrogen therapy was delayed. Estrogen therapy was recommended not to be initiated before the 12 yr of age and should ideally be started by the 15 yr of age (8). Estrogen therapy should be initiated at a low dose and increased gradually over a period of 2–3 yr (8).

The growth pattern in patients with TS should be improved by early diagnosis, early GH therapy and early estrogen therapy with a low dose. The quality of life for patients with TS may improve in Japan.

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