

Growth hormone treatment in Turner syndrome accelerates growth and skeletal maturation

C. Rongen-Westerlaken¹, J. M. Wit¹, S. M. P. F. De Muinck Keizer-Schrama², B. J. Otten³, W. Oostdijk⁴, H. A. Delemarre-van der Waal⁵, M. H. Gons⁶, A. Bot⁷, and J. L. Van den Brande¹
(Dutch Growth Hormone Working group)

¹Department of Paediatrics, University of Utrecht, Utrecht, The Netherlands

²Department of Paediatrics, University of Rotterdam, Rotterdam, The Netherlands

³Department of Paediatrics, University of Nijmegen, The Netherlands

⁴Department of Paediatrics, University of Leiden, Leiden, The Netherlands

⁵Department of Paediatrics, Amsterdam Free University, Amsterdam, The Netherlands

⁶Department of Paediatrics, University of Amsterdam, Amsterdam, The Netherlands

⁷Department of Endocrinology, Growth and Reproduction of the Erasmus University, Rotterdam, The Netherlands

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Abstract. Sixteen girls with Turner syndrome (TS) were treated for 4 years with biosynthetic growth hormone (GH). The dosage was 4 IU/m² body surface s.c. per day over the first 3 years. In the 4th year the dosage was increased to 6 IU/m² per day in the 6 girls with a poor height increment and in 1 girl oxandrolone was added. Ethinyl oestradiol was added after the age of 13. Mean (SD) growth velocities were 3.4 (0.9), 7.2 (1.7), 5.3 (1.3), 4.3 (2.0) and 3.6 (1.5) cm/year before and in the 1st, 2nd, 3rd and 4th year of treatment. Skeletal maturation advanced faster than usual in Turner patients especially in the younger children. Although the mean height prediction increased by 5.6 cm and 11 of the 16 girls have now exceeded their predicted height, the height of the 4 girls who stopped GH treatment exceeded the predicted adult height by only 0 to 3.4 cm.

Key words: Turner syndrome – Growth hormone – Growth

Introduction

Turner syndrome (TS) is a genetic disorder which is associated with short stature [5, 7, 13, 14]. The reason for this growth failure is unknown and cannot be explained by growth hormone (GH) deficiency [3, 6]. In spite of this, biosynthetic GH has been advocated for patients with TS. Preliminary results of GH treatment in girls with TS

have revealed an acceleration of statural growth, but so far few data are available about epiphyseal maturation during GH treatment.

In two earlier papers [9, 10] we have reported the response to biosynthetic methionyl human GH administered subcutaneously once daily at a dosage of 4 IU/m² body surface for a period of 1 and 2 years. We now present the 4-year results.

Patients and methods

Patients and therapy

Sixteen girls with TS entered the study. During the first 2 years the children received methionyl GH (Somatorm, Kabi, Stockholm, Sweden) and in the 3rd and 4th year they received recombinant authentic GH (Genotropin, Kabi, Stockholm, Sweden) in a daily dosage of 4 IU/m² body surface subcutaneously (equivalent to 0.9 (0.26) IU/kg body weight per week). If the height increment over the preceding 6 months was below 1 cm, the GH dosage was increased to 6 IU/m² in six patients after 36 to 45 months of treatment. GH treatment was discontinued if height increment was less than 0.5 cm over the previous 6 months. Low dose ethinyl oestradiol (0.1 µg/kg od, orally) was added in patients over the age of 13. In this report the results for the 13 patients who completed the 4-year period are given. The remaining three cases and also the two cases who discontinued treatment after 4-years of GH treatment are described individually.

Growth analysis

Height was expressed in SDS using the Dutch cross-sectional references [8] (SDS(XX)) and the references for Turner girls compiled by Lyon et al. (SDS(XO)) [5]. The growth velocity was expressed as cm/year and for comparison the velocity curves of girls with TS prepared by Ranke et al. were used [7].

The skeletal maturation (Tanner and Whitehouse 20-bones (TW-20), Tanner and Whitehouse-RUS (TW-RUS) [15] and Greulich and Pyle (GP) [1] was assessed by an experienced investigator. The advancement in bone age (TW-RUS) was compared with

Offprint requests to: C. Rongen-Westerlaken, University Hospital Nijmegen, Department of Pediatrics, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Abbreviations: GH = growth hormone; GP = Greulich and Pyle; TS = Turner syndrome; TW-RUS = Bone age according to the method of Tanner and Whitehouse (Radius, ulna and short bones)

Turner references [7]. For the present report we also analysed the roentgenographs serially with the GP atlas without using the scores of the carpal bones. This method was chosen because it has been shown that the maturation of carpal bones is not an important determinant in adult height prediction [16].

The relationship of the height increment to skeletal maturation was assessed by computing the height SDS for bone age: the "index of potential height (IPH)" described by Lenko [4] and Joss [2] by using mean (SD) height values for bone age (TW-RUS) in patients with Turner syndrome.

The prediction of adult height was calculated on the basis of the tables of Bayley-Pinneau and on the basis of extrapolating initial height SDS (projected adult height) [11].

For more details about patients and methods the reader is referred to the previous reports [9, 10].

Statistical analysis

Results are expressed as mean (SD) except if indicated otherwise. The paired Student *t*-test and the Wilcoxon matched paired signed rank test were used for the analysis of within-group changes. The correlations between various parameters were calculated by the Spearman correlation test.

Results

Growth

The results of the 13 patients who completed the 4-year treatment period are given in Table 1. Height expressed as SDS (XO) increased significantly during treatment. We observed a significant negative correlation ($P = 0.001$) between the increment in height (cm) after 4 years of treatment and age. The increment in height expressed as SDS for Turner references was not correlated with age.

Growth velocities during the 1st, 2nd and 3rd year were significantly higher than before treatment. The

growth velocity in the 4th year was not significantly different from that prior to treatment. In three of the six patients the increase in GH dosage led to a growth velocity increment of 0.9, 1.8 and 1.8 cm. However, this increase was of short duration (approximately 6 months). In the other three patients the growth velocity further decreased.

Four patients discontinued treatment and 1 patient changed treatment because of a poor growth velocity of 0.6 to 1.3 cm/year. The results are summarized in Table 2 and the individual growth curves are given in Fig. 1.

Skeletal maturation and predicted adult height

Skeletal maturation (TW-RUS) during the treatment period was 4.2 (1.3) years, significantly ($P = 0.001$) higher than expected in untreated patients with TS during the same period (3.1 (0.7)) [7]. In Fig. 2a and b skeletal maturation in relation to age is visualized, before and after 3 years of treatment. Three years was taken because during the 4th year several children discontinued treatment. The increment in the bone age (TW-RUS) was significantly negatively correlated with chronological age ($P = 0.01$). To exclude the effect of oestrogens on skeletal maturation we evaluated the data of the 6 patients who received only GH during 3 years. The bone age (TW-RUS) in these six patients increased by 3.8 (0.7) years, significantly more ($P < 0.05$) than the expected change (2.8 (0.2)) over this period.

The mean (SD) index of potential height for Turner girls increased significantly during treatment; this corresponds to an improvement of approximately 5 cm in final height. The mean (SD) height prediction (GP) increased by 5.6 (5.1) cm. Besides the four girls who stopped treatment, seven others exceeded their predicted adult height

Table 1. Selected growth variables over 4 years. Mean (SD)

	0	1	2	3	4
Height SDS (XX)	-3.8 (0.9)	-3.4 (1.1)**	-3.3 (1.2)**	-3.3 (1.3)	-3.1 (1.1)*
Height SDS (XO)	0.1 (0.8)	0.7 (0.8)***	1.1 (0.9)***	1.4 (1.0)***	1.5 (1.1)***
HV (cm/year)	3.4 (1.0)	7.6 (1.6)***	5.6 (1.1)***	4.8 (1.9)*	3.6 (1.5)
BA (TW20)	9.9 (1.3)	11.0 (1.3)	11.8 (1.0)	12.6 (0.9)	13.7 (0.8)
BA (TW-RUS)	9.9 (1.6)	11.4 (1.5)	12.3 (1.0)	13.3 (1.0)	14.1 (0.9)
BA (GP)	9.6 (1.4)	10.8 (1.1)	11.9 (1.0)	12.8 (0.8)	13.5 (1.0)
Height (SDS-BA)	-0.1 (0.6)	0.3 (0.7)*	0.6 (0.7)***	0.8 (1.0)**	0.8 (1.0)**
PAH	145.0 (5.1)	147.5 (5.4)*	147.5 (5.1)	149.3 (5.8)**	150.6 (5.8)**

Significantly different from the value before therapy

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2. Selected data of the 4 patients who discontinued treatment

Case	Before treatment				Stop treatment			
	Age	BA	Height (SDS)	PAH	Age	BA	Height (cm)	Height (SDS)
1	13.1	11.5	0.2	142.1	16.6	15.0	142.5	0.4
2	14.1	11.8	0.1	144.3	17.8	13.8	147.6	0.8
3	9.6	8.3	1.2	152.4	13.6	13.6	152.6	2.3
4	12.4	10.8	0.7	145.4	16.4	16.4	145.4	0.9

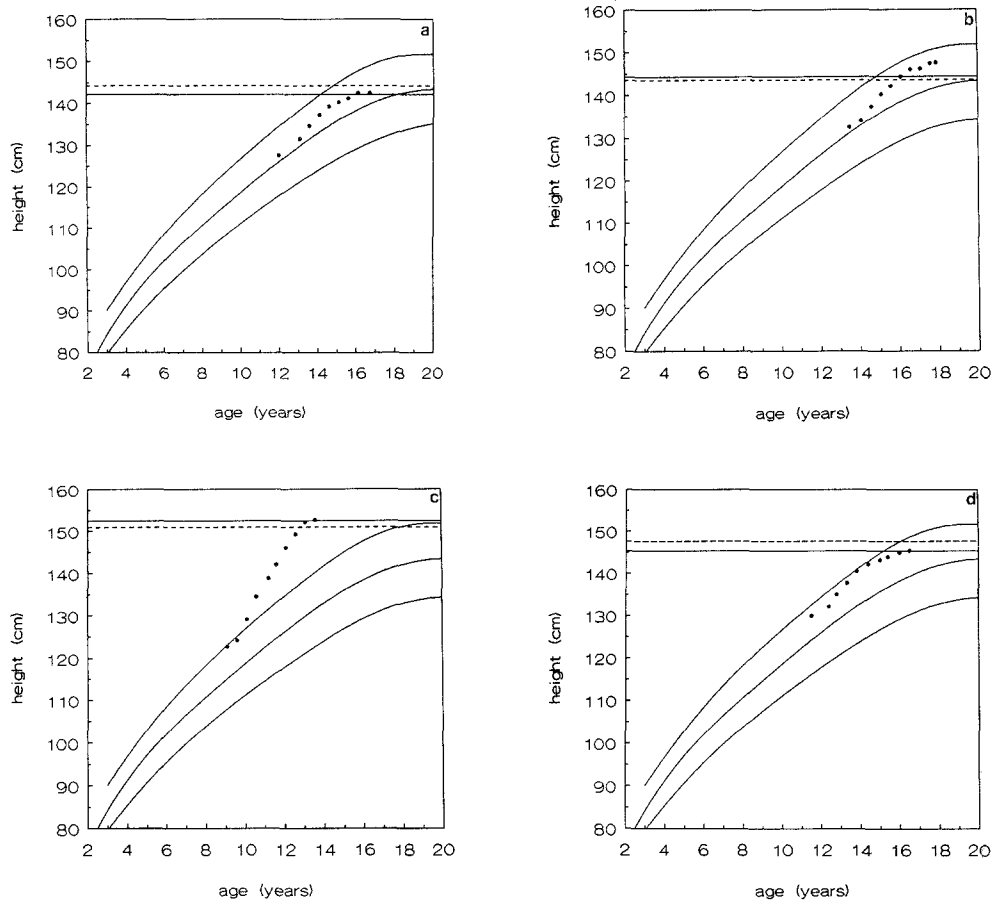


Fig. 1. Individual growth curves of the patients who discontinued treatment. (a–d representing cases 1–4) the *interrupted line* represents the adult height prediction based on the initial height SDS position and the *continuous line* represents the adult height prediction based on GP

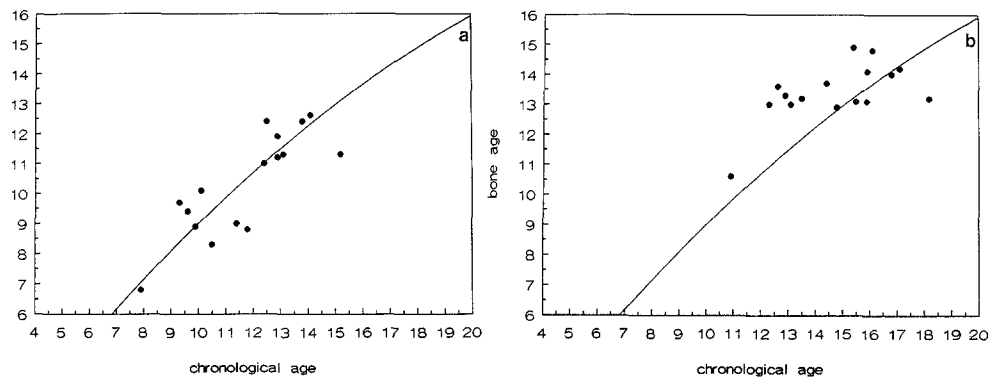


Fig. 2. Bone ages (TW-RUS) of all patients before (a) and after (b) 3 years of GH treatment plotted against the mean bone age for Turner girls in relation to age

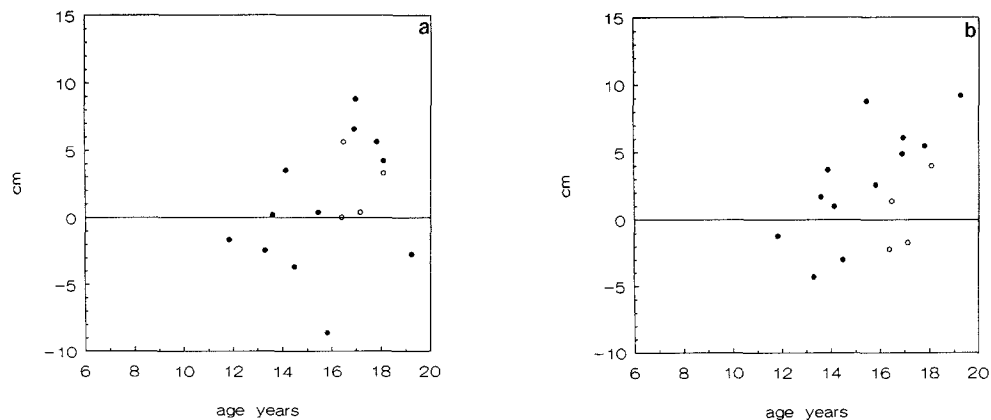


Fig. 3. The difference between actual height after 4 years of treatment and initially predicted adult height (a) and projected adult height (b) in relation to age. The *open circles* visualize the patients who discontinued GH treatment and the *closed circles* the patients who are still on treatment

by 0.03 to 8.8 cm. Eleven girls exceeded their projected adult height by 1.0 to 9.2 cm. The difference between statural height after 4 years of treatment and predicted or projected adult height in relation to age is shown in Figs. 3a and b.

In the four patients who discontinued treatment bone age (GP) at discontinuation of treatment varied between 13.9 and 15 years and height was 0 to 3.4 cm above their initially predicted adult height and -2.2 to $+4$ cm above their initially projected height. Growth velocity was poor (1.1 cm/year) in one patient during GH treatment despite a bone age of only 12.3 years and it was decided to add oxandrolone to the medication. Hereafter the growth velocity increased to 5.1 cm/year.

Intercurrent events

No relevant events were reported.

Discussion

Our results confirm that treatment with GH promotes growth in children with TS. GH treatment resulted in a significant increase in height velocity and in height Z-score (SDS) using Turner references. The increment in height SDS in our study after 3 years of treatment (1.4SD) is higher than found in the American study using GH alone in 3 injections/wk (0.9SD) but less than in the children on GH and oxandrolone (2.1SD) [11, 12]. In the 4th year there was little change in height SDS. There was a progressively diminishing effect of GH therapy on growth velocity.

To reach a higher final height, the increase in height must outweigh the increase in epiphyseal maturation. During treatment, skeletal maturation (TW-RUS) advanced 0.9 year faster than expected during the same period in untreated Turner patients [7]. The references for bone age (TW-RUS) [7] are based on girls with TS not treated with growth promoting substances, such as GH or oestrogens. The accelerated skeletal maturation in the six patients treated with GH alone strongly indicates that GH alone is able to accelerate skeletal maturation.

Before final height is actually reached, the effect of GH treatment on adult height can only be predicted. There are several methods for predicting adult height. Zachmann et al. [17] demonstrated that the GP method provided the most accurate height prediction in TS. However, only six children were investigated. The reliability of the "projected height" based on extrapolation of the height centiles was investigated by Lyon et al. [5], who found a slight underprediction averaging -0.6 cm. The results of the two prediction methods in our study before start of treatment were comparable: 144.1 (5.4) cm according to GP and 143.0 (4.7) by extrapolating height SDS. The prediction according to the method of GP increased by 5.6 cm during 4 years of treatment. After 4 years of treatment 11 of the 16 girls have exceeded their predicted adult height and also 11 of the 16 girls have exceeded their projected height. Furthermore there was an

increase in mean height SDS for bone age. These data suggest that final height might be increased as a result of treatment with GH.

During this period four patients stopped GH treatment. The final heights exceeded the predicted heights by 0 to 3.4 cm and the projected heights by -2.2 to 4 cm. These results are disappointing and are in contrast to the predicted increment of approximately 5 cm after 4 years of treatment in the whole group, although height at discontinuation of GH treatment is probably still somewhat lower than the future adult height. It is remarkable that one of the four patients stopped growing at a bone age at which growth should still be possible [7]. Another girl grew poorly on GH alone, although bone age was only 12.3 years. She responded very well after oxandrolone was added to the GH treatment. This illustrates that the growth promoting effect of oxandrolone is different in a qualitative sense from the effect of GH and it is well in line with the observation that GH and oxandrolone are additive in their effect [11]. It also indicates that on GH therapy growth may stop although the epiphyses in the hands have not yet fused, while further growth is possible with an anabolic steroid. Further research into this phenomenon is necessary because of the important clinical consequences.

In conclusion, in girls with TS GH increases height velocity but also accelerates skeletal maturation. The various prediction methods used for the 13 children who completed the treatment period of 4 years indicate that ultimate height will be approximately 5 cm higher than initially predicted adult height. However, there is considerable interindividual variation in the growth response to GH and the results in the four children who stopped GH treatment are disappointing. Therefore we feel that no firm conclusions can yet be drawn concerning the efficacy of GH therapy in terms of final height.

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