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ADULT HEIGHT IN TURNER SYNDROME GIRLS AFTER LONG-TERM GROWTH HORMONE TREATMENT

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Abstract We studied the adult height (AH) outcome, and factors likely to influence it, in Turner Syndrome (TS) girls treated with growth hormone (GH). A total of 25 TS girls treated with GH were compared with 10 TS girls not treated with GH. The percentage of girls who achieved normal third percentile was determined. Projected AH (PAH) was calculated according to height standard deviation score (HSDS) at the beginning of the treatment. Gain in height was determined as: AH – pretreatment PAH. The percentage of girls who achieved target range (midparental height±2 SD) was determined. Multiple linear regression models were fitted on baseline variables- chronological age (CA), midparental height (MPH) and HSDS; and treatment variables- duration of oestrogen-free GH therapy and duration of GH therapy+oestrogens. As for baseline data: median CA was 13.0 years (5.6-15.8). Mean HSDS was 0.25±1.1 SDS. PAH was 139.2±5.6 cm. MPH was 160.0±5.0 cm. As for follow up data: Median CA at onset oestrogens was 15.1 years (13.2-16.6). Median duration of GH therapy was 3.8 years (2.1-10.3). Median oestrogen-free GH period was 2.0 years (0.7-7.8), and median GH+oestrogens period, 1.8 years (1.0-3.2). Adult height: Mean AH was 150.4±7.0 cm in treated patients and 140.8±7.2 cm in the group not treated with GH (p=0.001). Fourteen (56%) girls achieved normal third percentile compared with an initially predicted 1 (4%). Gain in height was 11.2±3.7 cm. Thirteen (59%) girls reached an AH within target range. HSDS at the beginning of the treatment was the variable most strongly related to AH and duration of oestrogen-free GH period was the variable most strongly related to gain in height.

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

Resumen ***Talla adulta en pacientes con síndrome de Turner tratadas con hormona de crecimiento a largo plazo.*** Se estudió la talla adulta (TA) y los factores que pudieran influenciarla en niñas con síndrome de Turner (ST) tratadas con hormona de crecimiento (HC). Se compararon 25 pacientes con ST tratadas con HC y 10 niñas no tratadas. Se determinó: el porcentaje de niñas que alcanzó el tercer percentilo de la curva de normalidad, la talla adulta proyectada (TAP) de acuerdo al *score* de desvío estándar de talla (SDST) al inicio del tratamiento, la ganancia en talla (TA – TAP pretratamiento) y el porcentaje de niñas que alcanzó el rango genético (talla media parental ± 2 DS). Se ajustaron modelos de regresión múltiple sobre variables basales- edad cronológica (EC), talla media parental y SDST; y variables durante el tratamiento- duración del tratamiento con GH sin estrógenos y con GH+estrógenos. Resultados: datos basales: la EC mediana fue 13.0 años (5.6-15.8), el SDST 0.25 ± 1.1 SDS, la TAP 139.2 ± 5.6 cm y la talla media parental 160.0 ± 5.0 cm. Datos en el seguimiento: la EC mediana al inicio del estrógeno fue 15.1 años (13.2-16.6), la duración mediana del tratamiento con GH 3.8 años (2.1-10.3), del tratamiento con GH y sin estrógenos 2.0 años (0.7-7.8), y del tratamiento con GH + estrógenos 1.8 años (1.0-3.2). Talla adulta: la TA media fue 150.4 ± 7.0 cm en pacientes tratadas y 140.8 ± 7.2 cm en el grupo no tratado (p = 0.001). 14 niñas (56%) alcanzaron el tercer percentilo comparado con la predicción inicial de una niña (4%). La ganancia en talla fue 11.2 ± 3.7 cm. 13 niñas (59%) alcanzaron una TA dentro del rango genético. La variable que más se relacionó con la TA fue el SDST al inicio del tratamiento y con la ganancia en talla, la duración del tratamiento con GH libre de estrógenos.

Palabras clave: síndrome de Turner, hormona de crecimiento, talla adulta, estrógenos

Turner Syndrome (TS) is one of the most common human genetic disorders, affecting approximately one of every 2500 live born females[1, 2]. Growth failure is a cardinal feature of TS[3]. The mean adult height (AH) of Argentinian TS women not treated with growth hormone (GH) is 137.9 ± 5.1 cm[4], 21.1 cm below that of the general female population[5]. The short stature characteristic of TS is believed to result at least in part from haploinsufficiency of the short stature homeobox-containing gene, located in the pseudoautosomal region of the X and Y chromosomes at Xp22.3 and Yp11.3, respectively[6, 7].

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Recombinant human GH therapy has been widely used to enhance growth and thus to increase AH. Short-term results revealed a clear acceleration of height gain velocity when these patients were treated with supra-physiological doses of GH[8]. However, data about long-term height attainment have shown a variable outcome[2].

Because of ovarian dysgenesis, the induction of puberty is required in most of TS girls. Some authors have concluded that the addition of oestrogens to GH treatment did not affect AH[2, 9]. Other studies, however, have shown that oestrogen administration could decrease AH[10-12], particularly when started soon after initiation of GH therapy. Although it has been suggested that oestrogen replacement therapy should be postponed as late as possible to prolong the growth period[9], delaying puberty could have adverse psychological consequences[13] and may result in a decrease bone mineralization[14, 15]. Starting GH treatment at a young age allows a longer period of oestrogen-free GH treatment permitting the induction of puberty at an age-appropriate time[16, 17]. Despite these considerations, the optimal ages at which GH and oestrogens should be started are not clear at present.

We studied AH outcome and factors likely to influence it in a group of Argentinian TS girls treated with GH during childhood and followed-up until AH.

Materials and Methods

Twenty five TS girls followed longitudinally at the Endocrinology Unit of La Plata Children Hospital were studied. Patients fulfilling the following inclusion criteria were selected: 1) having karyotipe of TS, 2) having been treated with daily injections of GH for at least 2 years, 3) having undergone induced puberty, 4) having reached their AH, i.e. height velocity during the preceding year of less than 1 cm or a growth during the last 6 months of less than 0.5 cm.

The karyotipe distribution was: 45,X = 10 (40%); 45,X/46,Xi(Xq) = 6 (24%); 45,X/46,XX = 4(16%); 46,Xi(Xq) = 2 (8%); other karyotypes = 3 (12%).

All patients were treated with different registered trade marks of human recombinant GH at a dose of 0.33 ± 0.06 mg/kg/week, administered as daily sc injections. The GH dose was adjusted every 6 months according to body weight to keep the dose as close as possible to 0.33 mg/kg/week. The maximum GH dose was fixed at 2 mg/day.

Puberty was induced with low doses of echinus conjugated oestrogens (CEs). Starting dose was 0.625 mg, 2 days/week. The CEs were progressively increased every 6 months to reach an adult dose of 0.625 mg/day after 1 or 2 years of treatment. Cyclic progestagen therapy (medroxiprogesterone acetate, 10 mg daily for 10 days each month) was added 2.0 ± 0.7 years after the onset of CEs therapy to induce regular menstrual cycles.

Ten TS patients never treated with GH were matched to the TS girls treated with GH. There were no differences in the age of initiation of CEs treatment between patients and controls (15.2 ± 1.0 and 14.3 ± 2.3 years, respectively).

Height standard deviation scores (HSDS) were derived from published Argentinian standards for TS girls[4].

According to the Lyon height projection model[18], the HSDS at the beginning of the treatment was used to derive projected AH (PAH) on the assumption that in girls with TS there is a close relationship between height in the first decade and the AH.

The gain in height as a consequence of GH therapy was determined by subtracting the pre-treatment PAH from the recorded AH.

AH was defined when the height gain velocity during the preceding year was less than 1 cm or growth during the last 6 months less than 0.5 cm.

The midparental height (MPH) was calculated as: (father's height + mother's height)/2-6.0 cm. The target height range was defined as: MPH ± 2 SD. The percent of girls who achieved the target range was calculated. The remaining height deficit was considered to be: MPH-AH.

Bone age (BA) was determined at yearly intervals using the Greulich and Pyle method[19].

The effect of GH treatment was evaluated by: 1) comparing the AH of GH-treated patients with the AH of Argentinean TS standards and the historical controls not treated with GH, but supplemented with CEs, 2) calculating the percent of the girls who achieved the height of 149.2 cm considered to be a threshold for normal stature (Argentinean standard third percentile)[5], 3) considering the gain in height during GH treatment, 4) calculating the percent of the girls who attained the target range and the remaining height deficit (MPH – AH).

Two types of variables likely to influence the effect of GH treatment were calculated: baseline variables –chronological age (CA), BA, CA-BA difference, MPH and HSDS; treatment variables– duration of oestrogen-free GH therapy and duration of GH therapy + CEs.

The results are expressed as median (range) or mean (± SD).

The Student t test was used for comparisons between patients and controls.

Multiple linear regression models with backward selection were fitted to predict AH, gain in height and remaining height deficit. CA, CA-BA, MPH, HSDS, duration of oestrogen-free GH therapy and duration of GH therapy + CEs were tested as independent variables

Results

Twenty five TS girls started GH treatment at a median CA of 13.0 (Mn = 5.6-Mx = 15.8) years. The median BA was 11.0 (Mn = 3.0-Mx = 13.0) years, with a mean CA-BA difference of 2.4 ± 1.3 years. The mean HSDS matching Argentinian Turner height standards was 0.25 ± 1.1 SDS. Fig. 1 presents the individual CAs and heights of the girls at the start of therapy.

According to the Lyon projected method adapted to Argentinian TS standards, PAH at the start of GH therapy was 139.2 ± 5.6 cm.

The MPH calculated from normal population standards was 160.0 ± 5.0 cm.

The median CA at the onset of CEs replacement was 15.1 (Mn = 13.2-Mx = 16.6) years.

The median duration of GH therapy was 3.8 (Mn = 2.1-Mx = 10.3) years. The median CEs-free GH therapy period was 2.0 (Mn = 0.7-Mx = 7.8) years, and the median GH + CEs period, 1.8 (Mn = 1.0-Mx = 3.2) years.

Fig. 1 shows the individuals AHs of the TS girls in the present experimental group. The mean AH was 150.4 ± 7.0 cm.

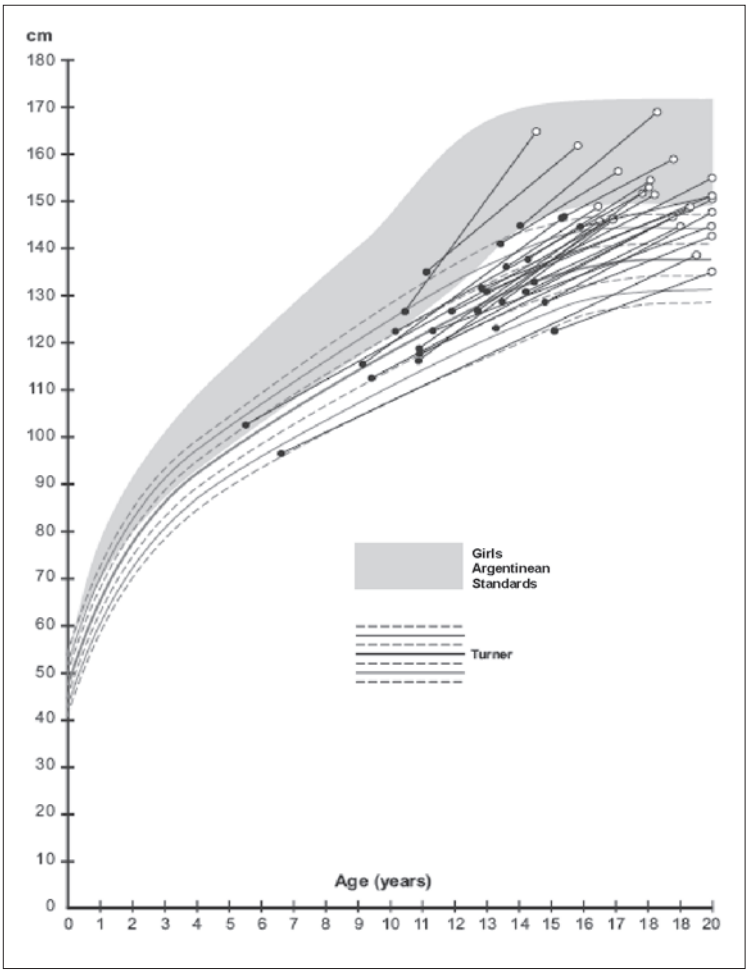

Fig. 1.– Height at start of growth hormone treatment and adult height in Turner Syndrome girls.

Expressed as SDS, the AH was -1.8 ± 1.1 with respect to the Argentinian normal standards, and 2.4 ± 1.4 Argentinian TS standards. In comparison with the Argentinian TS girls not treated with GH, the mean AH was 12.5 ± 7.0 cm higher (p = 0.000), with an HSDS increase of 2.4 ± 1.4 (p = 0.000).

The TS historical group not treated with GH reached a mean AH of 140.8 ± 7.2 cm, a value which was 9.6 ± 2.6 cm shorter than the AH of treated patients (p = 0.001).

On the basis of the PAH calculated by means of the Lyon PAH method, adapted to Argentinean TS girls not treated with GH, the gain in height during GH treatment (AH-PAH) was 11.2 ± 3.7 cm (p = 0.000), (5.88 ± 2.97 cm during CEs-free GH therapy period and 5.35 ± 2.38 cm during GH + CEs period).

With respect to the arbitrary height of 149.2 cm as a threshold for normal stature, 14 (56%) girls achieved this target compared to an initially predicted 1girl (4%).

The remaining height deficit (MPH-AH) was 10.2 ± 5.5 cm. Fifty percent of the girls reached an AH within target range (MPH ± 2SD).

In 20 patients, three multiple linear regression models were fitted to establish the influence of baseline variables (CA, CA-BA difference, HSDS, MPH) and treatment variables (duration of oestrogen-free GH therapy and duration of GH therapy + CEs) on AH, gain in height, and remaining height deficit (Table 1 a, b, c). The HSDS at the beginning of GH treatment, CA at the beginning of the treatment and the duration of oestrogen-free GH therapy period were related positively to the AH and inversely to the remaining height deficit. The MPH was related positively to the remaining height deficit. The CA at the beginning of the treatment, MPH, and the duration of oestrogen-free GH therapy period were positively related to the gain in height. The HSDS was the variable most strongly related to AH (p = 0.000) and to the remaining

TABLE 1.– *(a) Factors related to adult height, (b) Gain in height and (c) Remaining height deficit*

(a)		
Variables in the model	Coefficient	p-value
HSDS	6.001	0.000
CA	1.391	0.044
Duration of CEs free GH therapy	2.067	0.048
Constant = 125.501 (p=0.000)		

(b)		
Variables in the model	Coefficient	p-value
CA	1.790	0.028
MPH	0.251	0.031
Duration of CEs free GH therapy	2.590	0.019
Constant = -58.707 (p=0.059)		

(c)		
Variables in the model	Coefficient	p-value
HSDS	-5.277	0.000
CA	-1.740	0.048
MPH	0.780	0.003
Duration of CEs free GH therapy	-2.532	0.032
Constant = -84.830 (p=0.068)		

HSDS: height standard deviation score; CA: chronological age; CEs: conjugated oestrogens; MPH: midparental height

height deficit (p = 0.000) while the duration of the oestrogen-free GH therapy period was the variable most strongly related to gain in height (p = 0.019) The CA-BA difference and the duration of GH therapy + CEs were not related to the AH, the gain in height or the remaining height deficit (not shown).

Discussion

Growth hormone administration has become a common treatment for the short stature of the Turner syndrome. Although GH stimulates linear growth in TS patients, the effect on AH has remained uncertain. The present study shows that girls with TS treated with GH at a dose of 0.33 mg/kg/week have a significant increase in AH compared to TS women not treated with GH: the mean AH of our TS treated patients was 150.4 ± 7.0 cm, a value which is about 12.5 ± 7.0 cm taller than the AH reported in Argentinean Turner women not treated with GH (137.9 ± 5.1 cm)[4]. Our results are consistent with data from the literature for similar GH doses, in which the mean AH varied between 146.8 and 152.2 cm[2, 9, 12, 16, 17, 20-26]. To evaluate the effect of GH treatment, we also compared the AH to a historical control TS group. We found that the height of GH treated TS patients was 9.6 ± 2.6 cm taller than the controls. Furthermore, on the basis of the arbitrary height of 149.2 cm as a threshold for normal stature, 56% of the TS girls achieved this target compared with an initially predicted 4%. In addition, 50% the TS girls attained a height within the target range. Comparison of their AHs to the MPH revealed a remaining height deficit of 10.2 ± 5.5 cm. This result is similar to the observations of Massa et al[22] who found a remaining height deficit of 9.8 ± 6.4 cm. Taken together, our data and those from the literature clearly show a significant effect of GH treatment on the AH of TS girls[2, 9, 12, 16, 17, 20-26].

Although GH treatment seems to be effective in improving the AH in TS girls, a variability in the magnitude of the response to GH has long been recognised[22]. In the present study, we also found a large inter-individual variability with respect to the AH (range: 136.8-168.9 cm). A number of factors could potentially contribute to this variability, including pre-treatment features, such as the chronological or bone age at the initiation of therapy and the baseline height, as well as therapeutic details, such as the dose or duration of GH and the timing of oestrogen replacement. In agreement with other reports[10, 20-22] we found that height at the beginning of the treatment, parameter which is related to parental height, is one of the most important variables that could influence the AH. Hence, shorter TS girls at the beginning of GH treatment will end up with a shorter AH than will the taller TS girls. These findings demonstrate the importance of the genetic influences on growth. Indeed, TS girls may suffer intrauterine growth retardation. Accordingly, it has been described[26] that girls treated with higher doses of GH, corresponding to those used in non TS children with intrauterine growth retardation, the best results in terms of AH were obtained. Therefore, in view of the large variability in the GH response, GH treatment should be individualized in girls with TS syndrome in order to optimize the AH[22, 27, 28].

One of the key influences associated with improvement in the AH of TS girls is the age at the beginning of GH therapy. In accordance with the findings of Massa et al[22] and Pasquino et al[24], however, we did not observe that TS girls treated at a younger age could achieve a better AH. This discrepancy may be due to the delayed initiation of GH therapy in most of our patients. In fact, in this study the median age at the beginning of GH treatment was 13.0 (Mn=5.6-Mx=15.8) years. Such late initiation of therapy has diverse consequences: the patient spends most of her childhood as a short child, thus bearing the psychological burden of short stature with respect to her peers. Furthermore, height deviates progressively from normal with greater height deficit and shorter available time for therapy. In addition, because it has been shown that the duration of free-estrogen GH therapy period could influence height gain[2, 12, 16, 17, 22, 26, 29, 30], there is a tendency to postpone initiation of estrogen replacement.

For these reasons, GH treatment should be started as early as possible in order both to prevent progressive deterioration in height and to prolong pre-estrogen therapy period without causing a delay in puberty. Nearly all prior reports that have shown relatively modest gains in height have involved the study of patients with oestrogen replacement introduced shortly after the start of GH therapy. For example, the patients described by Taback et al[31] who had a gain in height of less than 5 cm, began oestrogens only 1.3 years after the initiation of GH therapy. Likewise, the 3 cm gain in height reported by Van de Broeck et al[32] was in patients beginning oestrogen therapy soon after starting GH therapy. In contrast, in our study, the gain in height was on the average 11.2 ± 3.7 cm. When we performed a linear regression analysis between factors that could influence gain in height, we found that the duration of free-oestrogen GH treatment period was the most important parameter involved. Our results are consistent with those reported in the literature which show that patients who received oestrogens early on relative to GH initiation fared worse in terms of their AH[2, 12, 16, 17, 22, 26, 29, 30]. Therefore, Turner syndrome should be early recognized in order to start GH therapy at a younger age allowing a longer free-oestrogen GH treatment period. Nevertheless, more data are required to delineate the optimal age to start GH treatment, taking into account the auxological as well as the psychological status of each individual TS girl.

In conclusion, this study has shown that GH treatment improves AH in TS girls, but with a wide variability on the response. The duration of the pre-oestrogen GH treatment period was a strong predictor for height gain. Therefore, early diagnosis of TS permits longer oestrogens-free GH treatment improving AH outcome and allowing a more age-appropriate initiation of oestrogen replacement.

Moreover, since the HSDS at the beginning of the GH treatment, which is related to the parental height, was a strong predictor for AH, this study demonstrates the importance of the genetic factors on GH treatment outcome.

Conflictos de interés: Ninguno a declarar.

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FAITH is a fine invention
For gentlemen who see;
But microscopes are prudent
In an emergency!

La FE es un gran invento
Para los caballeros que entienden;
Pero los microscopios son prudentes
¡En una emergencia!

Emily Dickinson (1830-86)

The Complete Poems of Emily Dickinson. Boston: Little, Brown, 1924; Bartleby. com 2000. Part One: Life. En: *http://www.bartleby.com/113/1056.html*; consultado el 26/8/2008