

Adult height in Turkish patients with Turner syndrome without growth hormone treatment

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SUMMARY: Bereket A, Turan S, Elçioğlu N, Hacıhanefioğlu S, Memioğlu N, Baş F, Bundak R, Darendeliler F, Günöz H, Saka N, Ercan O, Arslanoğlu İ, İşguven P, Yıldız M, Can Ş, Özerkan E, Çoker M, Darcan Ş, Özkan B, Orbak Z, Öztaş S, Palandüz Ş, Sezgin İ, Atabek E, Erkul İ, Erdoğan G. Adult height in Turkish patients with Turner syndrome without growth hormone treatment. *Turk J Pediatr* 2008; 50: 415-417.

Spontaneous adult height (AH) in Turner syndrome (TS) varies among populations. Population-specific AH data is essential to assess the efficacy of growth-promoting therapies in TS. A multicenter study was performed to establish AH of non-growth hormone (GH)-treated Turkish patients with TS.

One hundred ten patients with TS (diagnosed by karyotype) who reached AH (no growth in the previous year, or bone age >15 years) without receiving GH treatment were included in the study.

The average AH was found to be 141.6±7.0 cm at the age of 22.9±6.2 years, which is 18.4 cm below the population average and 16.4 cm below the patients' mid-parental heights. Bone age at start of estrogen replacement was 12.3±1.3 year. Karyotype distribution of the patients was 45X (43%), 45X/46XX (16%), 45X/46Xi (12%), 45XiXq (10%) and others (19%). When the patients were evaluated according to their karyotype as 45X and non-45X, no significant difference in AH was observed (142.4±6.9 cm vs 140.9±7.1 cm, respectively).

Adult height of non-GH-treated Turkish TS patients obtained in this study was comparable to that of other Mediterranean populations, but shorter than that of Northern European patients. Karyotype does not seem to affect AH in TS.

Key words: Turner syndrome, final height, adult height, karyotype, growth, growth hormone.

Turner syndrome (TS) affects about one in 1,500 to 2,500 live-born females. One of the most prevalent and salient features of the syndrome is short stature. Untreated women are approximately 20-21 cm shorter than normal women within their respective

populations, and the median adult height varies between 136 and 147 cm¹⁻¹⁰. Although a classical deficiency of growth hormone (GH) has not been generally demonstrated, recombinant human growth hormone (hGH) has been used to increase growth and final

height in girls with TS. In order to assess the efficacy of height-promoting therapies in TS, population-specific adult height data is needed in patients with TS who did not receive such therapies. Adult heights of Turkish TS patients without GH treatment have not been determined previously. A multicenter study was performed to establish such data in Turkish patients with TS.

Material and Methods

An invitation letter to participate in this study and study forms were sent to pediatric and adult Endocrinology, Gynecology and Genetics Departments of major university and teaching hospitals in Turkey. Information was requested for TS patients (diagnosed by karyotype) who reached adult height and never received GH treatment. Patients were accepted as reaching final height if there was no growth in the previous year, or if the bone age was >15 years. Standardized study forms were completed by the participating centers and transferred to the study coordinator (A.B.). These forms included questions about the karyotype, final height, chronological age, bone age, treatments received, age of initiation of estrogen treatment, parental heights, birth weight of the patient, and other relevant data. Sixteen centers participated by sending information about their patients. Data of 110 patients from 12 centers met the inclusion criteria (diagnosis of TS by karyotype, adult height attainment, and never treated with GH) and are presented here.

Results

A total of 134 patients were reported to the study coordinator. Twenty-four patients were excluded from the final analysis because of bone age equal to or less than 15 years. Thus, 110 patients from 12 centers were included in the final analyses. Mean age of the patients at the measurement of adult height was 22.9 ± 6.2 years (range 16-44 years). The average adult height was 141.6 ± 7.0 cm. Karyotype distribution of the patients was as follows: 45X (43%), 45X/46XX (16%), 45X/46Xi (12%), 45XiXq (10%), and others (19%). Analyses of the adult height according to the patients' karyotypes demonstrated no significant difference between those with karyotype of 45X and the others (142.4 ± 6.9 cm vs 140.9 ± 7.1 cm, respectively). However,

18 patients with 46, X i(Xq) karyotype in our study had a final height slightly shorter than the rest of the patients, although without statistical significance (139.3 ± 6.8 vs 142.1 ± 7.0 , respectively).

Mean birth weight of the patients was 2482 ± 922 g. Final height was correlated with birth weight ($r: 0.657$, $p < 0.005$). Mid-parental height had been reliably obtained only in 33 patients and was 158 ± 4.6 cm. There was no correlation between final height and mid-parental height.

Mean bone age at start of estrogen treatment was available for 16 patients and was 12.3 ± 1.3 years. No correlation was detected between the age of initiation of estrogen treatment and final height.

Discussion

Adult height of non-GH-treated Turkish TS patients found in this study (141.6 cm) was comparable to that of other Mediterranean populations (France 141-142.5 cm, Italy 142.5 cm) but shorter than that of Northern European (146.9 cm) patients^{1-4,7}. Studies from numerous countries have demonstrated that women with TS are approximately 20 cm shorter than the population average¹⁻¹⁰. Naeraa et al.⁷ demonstrated that mean final height was 146.8 cm in 76 TS women compared to 166.8 cm in the general female population in Denmark. The average adult height of healthy women in the Turkish population is 160 cm¹¹. Thus, the adult height of TS patients found in the present study is 18.4 cm (-3.1 SDS) below the population average and 16.4 cm (-2.8 SDS) below their mid-parental target height. The reason for a smaller difference between TS and normal women in our study can be explained by the effect of secular trend. Growth charts currently being used in Turkey were developed 33 years ago. Since then, a secular trend in height (0.96 cm/decade) was observed in the Turkish population between 1973 and 1997¹².

Karyotype did not make any difference with respect to adult height in our study. This was also the conclusion of many reports in the past^{7,9}. However, a recent Mexican study showed that adult height of TS patients was 136.9 ± 5.5 cm in general, but that it was affected by the particular karyotype: 46,Xi(Xq): 134.5 cm, 45,X: 137.3 cm, and 45X/46,XX: 139 cm¹⁰. The mean final height of Chinese

patients with TS was 142 cm, and patients with the 46, X, i(Xq) karyotype were found to be significantly shorter⁵. Similar results were obtained in a mixed group of Italian and Israeli patients with TS, in whom a deletion of the entire Xp segment [46,X,i(Xq)] was associated with the shortest height (median height 134.5 vs 142.5 for the rest of the patients)⁸. Results of these studies demonstrate that patients with TS who were disomic for Xp are significantly taller than patients who were monosomic for Xp. In line with the above-mentioned studies, 18 patients with 46, X i(Xq) karyotype in our study had a final height slightly shorter than the rest of the patients, although without statistical significance.

The timing of estrogen treatment was not influential in final height of the patients with TS in the absence of GH therapy in our study. In the study of Page¹³, comparison of patients with spontaneous and induced puberty to assess the effect of endogenous estrogen secretion on the final heights of patients with TS also revealed the same conclusions. Physiological and subphysiological endogenous secretion of estrogen in TS did not increase final height. Age of menarche showed no correlation with final height. Similarly, Sybert⁹ reported no significant deleterious effect on height with earlier induction of puberty with estrogens. The age at onset of puberty was not related to final height in GH-treated patients as well¹⁴.

Birth weight appeared to significantly influence final height in patients with TS in our study. This correlation was also observed by Naeraa et al⁷. However, mid-parental height did not correlate with final height in our study. This is most likely due to the sparse mid-parental height data in our study. Parental height and patient heights correlated significantly in the study of Rochiccioli et al². It has been reported that correlations between final height and parental heights, birth weight and birth length in women with TS were similar to those reported for normal women⁷.

We recognize the limitations of the study, which include collection of data from only the responding centers, as well as insufficient data regarding the timing of estrogen treatment and the influence of parental heights on the final height of the patients. However, the present data provides for the first time the final height of a large group of Turkish patients with TS without

GH treatment. Adult height of non-GH-treated Turkish TS patients obtained in the present study was similar to that of other Mediterranean populations and was not influenced by karyotype. Difference between adult height in patients with TS and the normal population was slightly less than that described in other countries, most likely due to secular trend. Since most children with TS currently receive GH therapy, this data will serve as a historical control group for assessment of growth-promoting therapies in our population.

REFERENCES

1. Ranke MB, Pfluger H, Rosendahl W, et al. Turner syndrome. Spontaneous growth in 150 cases and review of the literature. *Eur J Pediatr* 1983; 141: 81-88.
2. Rochiccioli P, David M, Malpuech G, et al. Study of final height in Turner's syndrome: ethnic and genetic influences. *Acta Paediatr* 1994; 83: 305-308.
3. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. *Arch Dis Child* 1985; 60: 932-935.
4. Mazzanti L, Nizzoli G, Tassinari D, et al. Spontaneous growth and pubertal development in Turner's syndrome with different karyotypes. *Acta Paediatr* 1994; 83: 299-304.
5. Low LC, Sham C, Kwan E, et al. Spontaneous growth in Chinese patients with Turner's syndrome and influence of karyotype. *Acta Paediatr* 1997; 86: 18-21.
6. Garcia Rudaz C, Martinez AS, Heinrich JJ, et al. Growth of Argentinian girls with Turner syndrome. *Ann Hum Biol* 1995; 22: 533-544.
7. Naeraa RW, Nielsen J. Standards for growth and final height in Turner's syndrome. *Acta Paediatr Scand* 1990; 79: 182-190.
8. Cohen A, Kauli R, Pertzalan A, et al. Final height of girls with Turner's syndrome: correlation with karyotype and parental height. *Acta Paediatr* 1995; 84: 550-554.
9. Sybert VP. Adult height in Turner syndrome with and without androgen therapy. *J Pediatr* 1984; 104: 365-369.
10. Robles Valdes C, del Castillo Ruiz V, Oyoqui J, Altamirano Bustamante N, de la Luz Ruiz Reyes M, Calzada Leon R. Growth, growth velocity and adult height in Mexican girls with Turner's syndrome. *J Pediatr Endocrinol Metab* 2003; 16: 1165-1173.
11. Neyzi O, Yalcindag A, Alp H. Heights and weights of Turkish children. *J Environ Child Health* 1973; 19: 5-13.
12. Nebigil I, Hizel S, Tanyer G, Dallar Y, Coskun T. Heights and weights of primary school children of different social background in Ankara, Turkey. *J Trop Pediatr* 1997; 43: 297-303.
13. Page LA. Final heights in 45,X Turner's syndrome with spontaneous sexual development. Review of European and American reports. *J Pediatr Endocrinol* 1993; 6: 153-158.
14. Massa G, Heinrichs C, Verlinde S, et al. Belgian Study Group for Pediatric Endocrinology. Late or delayed induced or spontaneous puberty in girls with Turner syndrome treated with growth hormone does not affect final height. *J Clin Endocrinol Metab* 2003; 88: 4168-4174.