

**Clinical Case Seminar**

**A4(1-5)**

## **In GH-treated girls with Turner syndrome height prognosis may sometimes exceed target height: a case report**

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### **Abstract**

A 5-years-old girl was diagnosed with Turner syndrome (TS) during a diagnostic work-up for short stature and dysmorphic features. Chromosome analysis revealed rare X-chromosomal abnormalities 46 X<sub>t</sub> (13:X) (p12;q24). GH therapy was started at the age of 5.5 years, and continued for 7 years with a fixed dose of 0.33 mg/kg/week, until adult height (AH) achievement. Six-monthly assessment of height standard deviation score and height velocity was performed under therapy, evaluating a prepubertal height gain of 31.7 cm and pubertal height gain of 20 cm. She achieved an AH of 159.3 cm, better than her target height (156.8 cm). In addition, she underwent spontaneous puberty at the age of 9.6 years, completed with menarche at 11.6 years and followed by regular menstrual cycles.

During GH treatment, IGF-1, insulin and glucose blood levels remained within a normal range.

The early onset of GH therapy may have allowed such a successful height outcome, with the achievement of full stature recovery during childhood and puberty in this TS case. The rare karyotype of our patient may also positively influenced her height final result.

**KEYWORDS:** Turner syndrome, GH therapy, adult height

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### **Introduction**

Turner syndrome (TS) is the most frequent chromosomal disorder in females, affecting about 3% of all females conceived and one in 2500 live births. Karyotype is necessary for diagnosis, documenting 45,X0 monosomy in approximately 50% of cases, followed by mosaicism or structural X-chromosome abnormalities, leading to a huge variety of clinical features.<sup>1</sup> No predictable genotype-phenotype correlation has been established yet, even if mosaicism is generally associated with milder phenotypes.<sup>1</sup> As a result, although absent pubertal development due to ovarian insufficiency is a very common occurrence, up to 30% of girls may undergo spontaneous puberty (only half of those completed with menarche) and 2-5% achieve spontaneous pregnancy, with higher prevalence in mosaic TS.<sup>2</sup>

Short stature is the most constant finding of the syndrome, affecting 80-100% of patients, even in absence of other clinical signs. Spontaneous TS growth pattern involves mild intrauterine growth

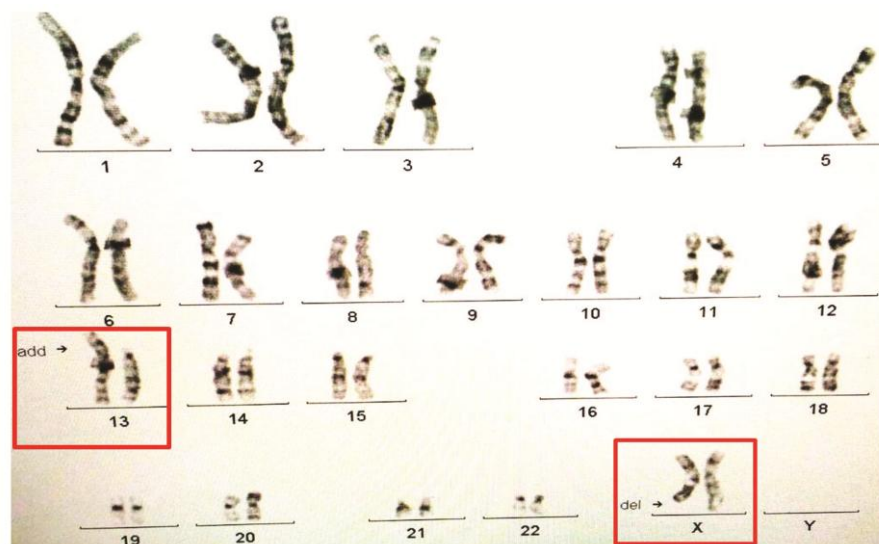
restriction, linear growth deceleration during infancy and childhood, and lack of pubertal growth spurt, resulting in an average adult height (AH) of 143 cm in untreated girls, about 20 cm below their peers and target height (TH). Although TS girls are not GH deficient, growth failure may be related to an impaired response to the hormone, which is treated effectively administering GH at supraphysiological doses (approximately double than that used in GH deficiency)<sup>3</sup>.

## Case Report

A 5-years-old girl was referred to our Centre of Pediatric Endocrinology for short stature and dysmorphic features. She was born full term and adequate for gestational age (AGA), with a remote medical history of congenital heart disease (patent ductus arteriosus) and chronic otitis. On physical examination, her stature was at -2.11 SD (101 cm) versus TH of -1.15 SD (156.8 cm), with abnormal sitting height/standing height ratio (0.56).

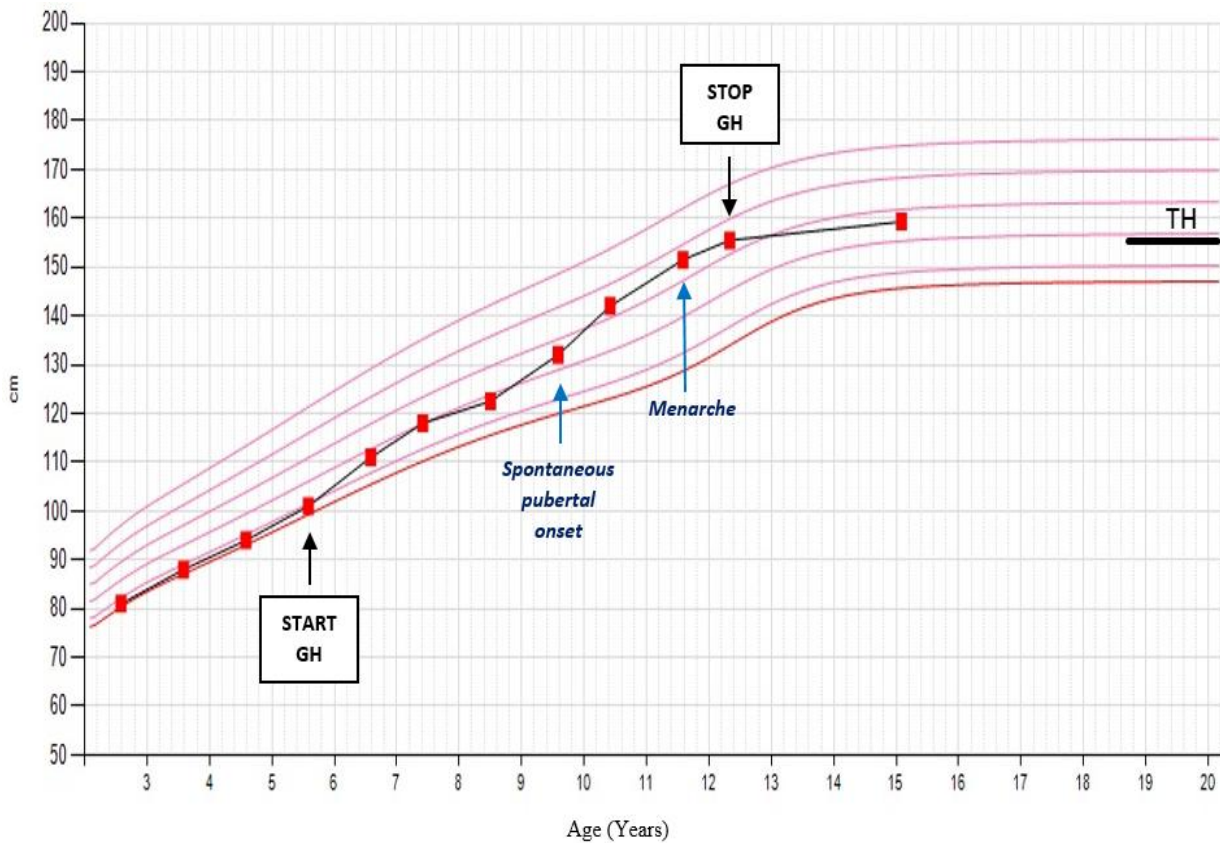
Her dysmorphic phenotype included ocular hypertelorism, low-set ears, ogival palate, trident hairline, short fourth metacarpal and cubitus valgus. Chromosome analysis revealed a rare TS karyotype (figure 1), characterized by X-autosomal translocation 46 Xt (13:X) (p12;q24).

Figure 1. A rare form of TS karyotype: X-autosomal translocation 46 Xt (13:X) (p12;q24).



GH therapy was started at the age of 5.5 years, as soon as the diagnosis was made. Assessment of height standard deviation score and height velocity (HV) was performed every six months under therapy, evaluating a prepubertal height gain of 31.7 cm during the first 4 years of GH therapy, and pubertal height gain of 20 cm in the following 3 years. GH was administered for 7 years at the fixed dose of 0.33 mg/kg/week, until the achievement of an AH of 159.3 cm, better than her TH (figure2). Moreover, at the age of 9.6 years she underwent spontaneous puberty, completed with menarche at 11.6 years and followed by regular menstrual cycles.

Figure 2. Grow chart of our patient: height monitoring for 7 years under GH therapy.



During GH treatment we did not observe any side effects and IGF-1, insulin and glucose blood levels remained within a normal range.

## Discussion

It is well established that GH therapy is effective in accelerating height velocity and increasing AH in TS. According to the Canadian and North American RCTs, mean AH gain was of 5-8 cm in treated girls compared to randomized untreated or placebo controls<sup>4-5</sup>, while European studies reported a mean height gain of 7-12 cm versus baseline predicted AH<sup>6-8</sup>, with wide individual variability.

Despite growth-promoting therapy, TS girls AH is generally at the lowest range for female population standards<sup>3</sup>.

To our knowledge, there are no data from the literature reporting such a successful height outcome as observed in our patient, especially in cases with spontaneous puberty occurrence, which is often a negative predictive factor for AH improvement in TS.<sup>1</sup> To date, only a recent published Japanese study described similar results in a patient treated with early GH-therapy and

ultra-low estrogen dosage, achieving an AH of 159.2 cm (with TH of 157 cm).<sup>9</sup>

There is no doubt that GH-therapy is an effective growth-promoting strategy in TS; however, the great variability in the long-term outcomes suggests that many factors play an important role on its efficacy. Major determinants of AH improvement are age at initiation and duration of GH therapy, which should be started as soon as growth failure is observed and prolonged until little growth potential remains (bone age $\geq$ 14 years and HV $<$ 2cm/year). Other positive predictors include height at initiation of therapy, TH, growth responsiveness during the first year of therapy, higher GH doses and longer period of treatment before induction of puberty.<sup>10-12</sup>

In conclusion, the case we described highlights for the first time a very successful height outcome in TS, even in a girl with spontaneous pubertal development. The early onset and long duration of GH therapy may have allowed the achievement of full stature recovery during childhood and puberty in this case. Arguably, our patient's karyotype positively influenced her height outcome, but no data from the literature are available to verify this correlation since X-autosomal translocation is mentioned as an extremely rare TS karyotype.<sup>1</sup> Moreover, no convincing evidence of potential affection of chromosomal abnormalities on final height has been clearly elucidated yet.<sup>12</sup>

**Conflicts of Interest:** There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

## References

1. International Turner Syndrome Consensus Group (2017) Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*, 177, G1-G70. doi:10.1530/EJE-17-0430.
2. Pasquino, A.M., Passeri, F., Pucarelli, I., Segni, M., Municchi, G. (1997) Spontaneous pubertal development in Turner's syndrome. *J Clin Endocrinol Metab*, 82, 1810-3. doi: 10.1210/jcem.82.6.3970.
3. Baxter, L., Bryant, J., Cave, C.B., Milne, R. (2007) Recombinant growth hormone for children and adolescents with Turner syndrome. *Cochrane Database of Systematic Reviews*, 1, CD003887. doi: 10.1002/14651858.CD003887.pub2.
4. Stephure, D.K., Canadian Growth Hormone Advisory Committee. (2005) Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab*, 90, 3360-6. doi:10.1210/jc.2004-2187.
5. Ross, J.L., Quigley, C.A., Cao, D., Feuillan, P., Kowal, K., Chipman, J.J., Cutler, G.B. Jr. (2011) Growth hormone plus childhood low-dose estrogen in Turner's syndrome. *N Engl J Med*, 364, 1230-42. doi:10.1056/NEJMoa1005669.
6. Carel, J.C., Mathivon, L., Gendrel, C., Ducret, J.P., Chaussain, J.L. (1998) Near normalization of final height with adapted doses of growth hormone in Turner's syndrome. *J Clin Endocrinol Metab*, 83, 1462-6. doi:10.1210/jcem.83.5.4777.
7. Sas, T.C., de Muinck Keizer-Schrama, S.M., Stijnen, T., Jansen, M., Otten, B.J., Hoorweg-Nijman, J.J., Vulsma, T., Massa, G.G., Rouwe, C.W., Reeser, H.M., Gerver, W.J., Gosen, J.J., Rongen-

Westerlaken,C.,Drop,S.L. (1999) Normalization of height in girls with Turner syndrome after long-term growth hormone treatment:results of a randomized dose-response trial. *J Clin Endocrinol Metab*, 84,4607-12 . doi:10.1210/jcem.84.12.624.

8. Van Pareren,Y.K., de Muinck Keizer-Schrama,S.M., Stijnen,T., Sas,T.C., Jansen,M., Otten,B.J., Hoorweg-Nijman,J.J., Vulmsa,T., Stokvis-Brantsma, W.H., Rouwé,C.W., Reeser,H.M, Gerver,W.J., Gosen,J.J., Rongen-Westerlaken,C., Drop,S.L. (2003) Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab*, 88,1119-25. doi:10.1210/jc.2002-021171.

9. Hasegawa,Y., Ariyasu,D., Izawa,M., Igaki-Miyamoto,J., Fukuma,M., Hatano,M., Yagi,H., Goto,M. (2017) Gradually increasing ethinyl estradiol for Turner syndrome may produce good final height but not ideal BMD. *Endocr J*,64,221-227. doi:10.1507/endocrj.EJ16-0170.

10. Wasniewska,M., De Luca,F., Bergamaschi,R., Guarneri,M.P., Mozzanti,L., Matarazzo,P., Petri,A., Crisafulli,G., Salzano,G., Lombardo,F. (2004) Early treatment with GH alone in Turner syndrome: prepubertal catch-up growth and waning effect. *Eur J Endocrinol*, 151, 567-72. doi: 10.1530/eje.0.1510567.

11. Wasniewska,M., Aversa,T., Mazzanti,L., Guarneri,M.P., Matarazzo,P., De Luca,F., Lombardo,F., Messina,M.F., Valenzise,M. (2013) Adult height in girls with Turner syndrome treated from before 6 years of age with a fixed per kilogram GH dose. *Eur J Endocrinol*, 169,439-43.doi: 10.1530/EJE-12-1032.

12. Ranke,M.B., Lindberg,A., Ferrández Longás,A., Darendeliler,F., Albertsson-Wikland,K., Dunger,D., Cutfield,W.S., Tauber,M., Wilton,P.,Wollmann,H.A., Reiter,E.O.; KIGS International Board. (2007) Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Pediatr Res*, 61,105-10. doi:10.1203/01.pdr.0000250039.42000.c9.



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***Communicated and received Novembre 15, 2017, revised November 30, 2017, published on line December 20, 2017***