

COMMENTARY

Growth-Promoting Strategies in Turner's Syndrome

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TURNER'S syndrome is an important cause of short stature in girls and primary amenorrhea in young women. First described in 1930 by Otto Ullrich (1) in Germany and subsequently in 1938 by Henry Turner (2) in the United States, it is the most common sex-chromosome abnormality in females, affecting an estimated 3% of all females conceived. However, only 1 in 1000 embryos with a 45,X karyotype survives to term, accounting for about 15% of all spontaneously aborted fetuses (3). Thus, the incidence of the loss of all or part of an X chromosome varies from 1:2000 to 1:5000 in liveborn phenotypic females (3–8). In a recent prospective study of 17,038 newborn girls born in Aarhus, Denmark, nine karyotypes consistent with Turner's syndrome were detected, for an incidence of 1:1893 live female births (8). There are currently estimated to be from 50,000 to 75,000 girls and women with Turner's syndrome in the United States alone (9).

Molecular studies have shown that the maternal X is retained in two thirds of patients with Turner's syndrome and the paternal X in the remaining one third (10, 11). More than half of all patients with Turner's syndrome have a mosaic chromosomal complement, (e.g., 45,X/46,XX) (12–14). Mosaicism with a normal cell line in the fetal membranes may be necessary for adequate placental function and fetal survival (15, 16).

The identification of mosaicism depends directly on the method of ascertainment. It varies from 34% with conventional cytogenetic techniques to 60% with fluorescence *in situ* hybridization techniques to 74% in a study in which RT-PCR assays were used (17).

Many patients with Turner's syndrome lack only part of one X chromosome, and the Turner's syndrome phenotype can be seen with a variety of structural abnormalities, such as rings, isochromosomes, or terminal deletions. A rare but very informative class of Turner's syndrome includes patients who have deletions of the Y chromosome that remove the testes determining gene *SRY*. These individuals develop as females. Based on this finding and the fact that males require only one X chromosome for normal development, Ferguson-Smith (13) hypothesized more than 30 yr ago that copies of Turner's syndrome genes are also present on the Y chromosome.

Specific localization of Turner's syndrome genes proved elusive until recently when one group successfully demonstrated that a gene located in the pseudoautosomal region (PAR 1) at the tip of the short arm of the X chromosome (Xp 22.3) is related to short stature in Turner's syndrome. This pseudoautosomal deletion encompassing a novel homeobox gene, *SHOX* (short stature homeobox containing gene on the X chromosome), is associated with short stature in Turner's syndrome and also with some cases of idiopathic short stature (18). Independently, the same gene was identified by a different group and was termed pseudoautosomal homeobox-containing osteogenic gene (*PHOG*). The *SHOX* gene encodes a homeodomain-containing protein that most likely functions as a transcription regulator. Dosage sensitivity is a common feature of such regulatory genes in the pseudoautosomal region. They escape X inactivation and have functional homologs on the Y chromosome (19–21). It is, therefore, hypothesized that haploinsufficiency of the *SHOX* gene is the underlying cause of growth impairment in patients with Turner's syndrome (18, 22).

The tips of the short arms of the chromosomes X and Y are logical sites for Turner's syndrome genes, as sex chromosomes undergo meiotic recombination within the pseudoautosomal region and all genes in this region that have been examined escape X inactivation. Characterization of *XY_p* females provides additional support for the hypothesis of a distinct Turner's syndrome stature locus: most of these patients have unbalanced X,Y translocations and, in the most fully documented patients with this karyotype, two intact copies of the pseudoautosomal region are present. It is not surprising that these patients attain normal stature despite the presence of features consistent with Turner's syndrome. A 700-kb interval in the pseudoautosomal region is, therefore, the most probable site for a Turner's syndrome stature locus, and *SHOX* is an excellent candidate for a Turner syndrome stature gene (18, 23).

Studies that have examined the relationship between the chromosomal and karyotypic abnormalities and clinical findings in patients with Turner's syndrome have been disappointing.

Endocrine Manifestations of Growth Failure

Short stature is the only clinical finding invariably associated with the 45,X karyotype; it also is the only phenotypic abnormality present in virtually 100% of patients (24). Mean

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adult height of women with Turner's syndrome ranges between 136.7 cm (Japan) and 146.9 cm (Germany) (25).

Many patients with Turner's syndrome are also stocky and have a squarely shaped chest. Affected neonates have congenital lymphedema of the hand and feet, a webbed neck, and a low hairline. Short stature is the single most common physical abnormality in Turner's syndrome, and individuals not treated with growth-promoting techniques achieve an adult stature 20 cm shorter than that of the normal population. The height of patients with Turner's syndrome, when plotted on growth curves specific for this disorder, show that growth velocity declines often as early as 2–4 yr of age below the growth curve normal for females.

In patients with Turner's syndrome, adult height is short due to poor growth rates *in utero* in infancy and childhood and a pronounced lack of pubertal growth. The normal pubertal growth spurt does not occur in Turner's syndrome. Bone age is further delayed during adolescence due to the lack of estrogenic influence on the skeleton. However, adult final height of untreated patients is not greater in the approximately 25% of girls with Turner's syndrome who experience spontaneous puberty. Final height of untreated patients correlated significantly with midparental height ($r = 0.7$) (26). Recent data (27) indicate that growth failure is already present in the first 2 postnatal yr. Furthermore, growth charts for individuals 2–18 years of age demonstrate that the majority of girls with Turner's syndrome are below the fifth percentile for height by the age of 2 yr. Davenport *et al.* (27) observed that mean height SDS fell from -0.5 at birth to -1.7 at age 1 yr and -2.0 at age 1.5 yr. Management of growth failure is now a common part of pediatric endocrine therapy for these patients although diagnosis and initiation of therapy is still, unfortunately, inexcusably delayed for many patients.

How short stature in girls with Turner's syndrome is treated will affect many other aspects of this disorder, including the age at which estrogen replacement can be begun, socialization, and academic achievement.

There is no need to measure serum GH levels, except possibly in those who are growing more slowly than the average patient with Turner's syndrome. Serum GH is usually normal, and measurement will not affect therapy. Third party payers should, therefore, not require GH secretory assessment of Turner's syndrome before initiation of GH therapy.

Growth-Promoting Strategies in Turner's Syndrome

In 1983 a multicenter, prospective, randomized trial of human GH, alone or in combination with oxandrolone, was initiated in the United States (28). In 1997, after 12 yr, all subjects had completed GH therapy, and an evaluation of the impact of therapy on their adult height could be performed. Seventy-two girls were initially enrolled. At entry their chronological age ranged from 4.7–12.4 yr, with a mean of 9.3 yr. Mean skeletal age, according to standards of Greulich and Pyle, was 8.0 yr, with a maximum bone age of 11.2 yr. Heights at entry were at least 1 SD below the mean for normal girls of equivalent chronological age, and the annualized growth rate was less than 6 cm/yr.

Subjects were randomly assigned to one of four study arms: 1) a control group receiving no therapy; 2) oxandrolone (125 mg/kg-day; 3) human GH (125 mg/kg three times per week; 4) combination of human GH and oxandrolone at the doses stated previously.

After 1 to 2 yr, in the first phase of the study, subjects receiving GH alone continued to receive this treatment, whereas all other subjects received the combination of oxandrolone, although the latter at a reduced dose of .625 mg/kg-day. After 2 yr in the second phase of the study, recipients of GH alone continued to receive only GH at a total weekly dose of 0.375/mg·kg, which was divided into seven daily administrations. Subjects receiving GH plus oxandrolone were randomly assigned to continuing combination treatment with GH administered either daily or three times per week at the same total weekly dose of 0.375 mg/kg. Estrogen therapy was delayed in all subjects until they had reached a minimum chronological age of 14 yr and had been in the study at least 3 yr. Administration of conjugated estrogens was begun at 0.3 mg/day (Premarin) and increased to 0.625 mg/day after 6 months. After 1 yr, estrogen replacement was given cyclically and progesterone was added.

The mean adult height for recipients of GH alone was 150.4 ± 5.5 cm, 8.4 ± 4.5 cm above the projected adult heights. Thus, 58 of the 62 GH-treated subjects (94%) attained adult height greater than their projected adult heights (29). For the 43 subjects treated with a combination of GH and oxandrolone, the mean adult height was $152.1 \text{ cm} \pm 5.9 \text{ cm}$, 10.3 ± 4.7 cm taller than their projected adult heights. Oxandrolone, a nonaromatizable androgen, is indicated particularly in Turner's syndrome patients ascertained late with a limited amount of time for growth promotion available. In young children (under age 8 or 9 yr), it may not be necessary. In any case, after approximately 4 yr of therapy, growth velocity in the combination group (GH and oxandrolone) was identical to the GH alone group. These results compare favorably not only with the matched American control group, but also with previous reports of final heights of girls with untreated Turner's syndrome from the United States and many other countries (30–34). The mean adult height attained by a retrospective control group as part of this study was 144.2 ± 6.0 cm.

These results compare also favorably with preliminary data from a second United States study in which 29 girls receiving GH alone (plus estrogen replacement at 15 yr of age) achieved a mean height at $16.3 \pm .9$ yr of 150.4 ± 6.0 cm, 8.4 ± 4.3 cm above their pretreatment projected adult heights (35, 36). The patients whose estrogen therapy was delayed until age 15 grew an average of 8.4 cm beyond their projected height, whereas those girls starting after age 12 grew only 5.1 cm, on average, beyond their projected height.

A multivariate analysis was used to examine several factors that might influence the gain in stature. The number of years of GH therapy before estrogen treatment was a strong predictor. These data show that the early induction of estrogen has a significant negative impact on adult height. A variety of published studies have reported that GH therapy results in an average height gain of 5–10 cm, a range that represents a surprising variability in outcome (37–41). It seems that at least some of this variability may be due to differences in the ages in which estrogen therapy was begun

in these patients. Some of the reports that showed that patients who had more modest apparent gains in final height also had relatively short periods of GH administration before the introduction of estrogen therapy (39, 41).

Several studies that did not achieve such reassuring gains in final height (39, 41) were also using lower GH doses than the United States study groups. This became particularly apparent in several studies carried out by the Dutch Advisory Group on Growth Hormone (42, 43). Their final assessment clearly shows that in a carefully conducted frequency response and dose-response study the increased dose of GH led to impressive increases in final height, exceeding even the data seen in the United States study. Seven-year results and preliminary final height data of this ongoing dose-response study are now available.

These investigators treated 68 patients with chronological ages between 2 and 11 yr and heights below the 50th percentile for healthy Dutch girls. The dosages used were 1.3 mg/m²·day (0.23 mg/kg·week) to as high as 2.7 mg/m²·day (*i.e.*, 0.6 mg/kg·week). It is clear from the Dutch data that there is a dose-response curve and that patients with the higher GH dose grew significantly better.

During the 1st yr of treatment, all groups received GH at a dose of 1.3 mg/m²·day; in the 2nd yr, two subgroups were switched to doses of 2 mg/m²·day, and a third group was switched to 2.7 mg/m²·day in the 3rd yr. All were then treated at these doses for the remainder of the study period. After 7 yr of GH treatment, mean final heights of 25 of the girls were 159.1, 161.8, and 162.7, respectively, for the three groups. These investigators concluded that after 7 yr of GH treatment most girls with Turner's syndrome are growing within the height range for healthy normal girls. GH treatment increased predicted adult height, and their preliminary results showed that long-term GH treatment results considerably increase final height gain. For a review of these study results, see Table 1.

It should be pointed out that final height data reported by many groups (39–44) in different countries using different study protocols are still most likely conservative estimates of the effect of therapeutic intervention with GH on height potential in patients with Turner's syndrome. Many of the patients were enrolled at older ages, thus limiting the duration of GH therapy. GH doses used were often well below the 0.375 mg/kg·week used in the United States studies (29). Some investigators began estrogen replacement as early as 14 yr and used relatively high dosages of estrogen. This will only hasten epiphyseal fusion and, thus, compromise height

potential. Large-scale postmarketing studies have reported final heights that are more modest (44). These results, which show nonetheless significant gains in final height, are most likely due to the same factors cited above.

Compliance with medical therapy such as daily injections of GH is sometimes suboptimal. Anticipated introduction of long-acting GH therapy may obviate that concern to some extent.

Lastly, final height was reported by some investigators that may not have been the true final height for some subjects.

In general, treatment was remarkably safe. The following possibly related adverse events were observed infrequently: intracranial hypertension, slipped capital femoral epiphysis, progression of preexisting scoliosis, edema, and otitis media (45, 46). Preliminary studies of increased serum lipoprotein (a) levels after GH treatment were not confirmed in larger series (47, 48). Although glucose levels stay normal, insulin levels rise both pre- and postprandially. Hemoglobin A1c levels stay in the normal range. Insulin levels decline in many patients after GH is discontinued (49).

Conclusions

Although the treatment with GH is invasive, laborious, and expensive, the adult height of patients with Turner's syndrome can be improved significantly, and final heights of 150 cm are a reasonable goal (29). Early diagnosis and early intervention are still the cornerstones for further improvements in the treatment of growth disorders in patients with Turner's syndrome.

Spontaneous puberty occurs in about 25% of patients with Turner's syndrome (50). Final height in those with spontaneous puberty is not different from those with no puberty.

Thus, physicians should consider the diagnosis of Turner's syndrome in any girl with an unexplained failure to thrive or with short stature even during the 1st yr of life. Therapy should be initiated when the child falls below the normal female growth curve. This may be as early as 2–4 yr of life, and it is in those patients that predictably the best outcomes, as far as height is concerned, will ensue.

Earlier correction of the height deficit might then also allow earlier introduction of physiological doses of estrogen replacement, thus achieving for most girls with Turner's syndrome relatively normal growth and sexual maturation.

A meta-analysis is underway to analyze and reconcile historical treatment data from various studies (51). This study will undoubtedly confirm the efficaciousness of GH therapy in

TABLE 1. Final height in Turner's syndrome

	Dose (mg/kg/week)	Final height (cm)	Gain (cm)	Duration of treatment (yr)
United States study ^a (Genentech)				
GH (n = 17)	0.375	150.4 ± 5.5	8.4 ± 4.5	7.6 ± 2.2
GH + Oxandrolone (0.0625 mg/kg·day) (n = 43)	0.375+	152.1 ± 5.9	10.3 ± 4.5	6.1 ± 1.9
United States study ^b (NCGS) (n = 622)	0.35	148.3 ± 5.6	6.4 ± 4.9	3.7 ± 1.9
Dutch study ^c (dose response) (n = 68)	0.46 to 0.63 (mg/kg·week)	159.1 (148.3–172.4) to 162.7 (154.3–170.3)	12.5 (7.8–15.7) to 16.0 (10.2–24.8)	7

^a RG Rosenfeld, *et al.* (29).

^b L Plotnick, *et al.* (44).

^c TC Sas, *et al.* (42).

Turner's syndrome as long as patients are treated early with appropriate doses of GH for prolonged periods of time.

The care of patients with Turner's syndrome continues, of course, well beyond growth promotion and requires long-term estrogen and progestin replacement. The care should be placed in the hands of physicians knowledgeable about the natural history of the unique medical and behavioral problems and medical needs associated with the syndrome (9). To improve the quality of life requires a team approach of physicians together with the efficient and compassionate support groups of the Turner's Syndrome Society both in the United States and abroad.

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