

Growth and growth hormone treatment in Turner syndrome

Marsha L. Davenport^{a,*}, Sabine M.P.F. de Muinck Keizer-Schrama^b

^a *Pediatric Endocrinology, CB #7039, 3341 Medical Biomolecular Research Bldg., University of North Carolina, Chapel Hill, NC 27599-7039, USA*

^b *Department of Pediatrics, Division of Endocrinology, Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands*

Abstract. Short stature is a universal clinical feature of Turner syndrome (TS). Growth failure begins in fetal life and adults with TS average 20 cm shorter than the normal female population. GH is effective in improving height velocity and final adult stature in TS. The most important factors determining GH efficacy are young age at initiation of therapy, long duration of therapy, daily administration and adequate dosing. GH should be initiated as soon as growth failure is demonstrated, hopefully while the child's stature is still in the normal range. Most girls with TS diagnosed in infancy or early childhood can now anticipate a normal or near-normal height. © 2006 Elsevier B.V. All rights reserved.

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1. Introduction

Short stature is considered the most universal clinical feature of Turner syndrome (TS) [1]. The following summarizes our current understanding of the pattern of abnormal growth in TS and the appropriate use of growth hormone to normalize growth velocity and final adult stature in this population.

* Corresponding author. Tel.: +1 919 966 4435; fax: +1 919 966-2423.

E-mail address: mld@med.unc.edu (M.L. Davenport).

2. Growth

2.1. Linear growth pattern

Girls with TS are typically born with mild intrauterine growth retardation and grow slowly during infancy [2–5]. In a study of longitudinal growth in full-term girls with TS, mean length/height SDS fell from – 0.5 at birth to – 1.5 at age 1 year and – 1.8 at age 1.5 years [4]. Girls with TS have a delayed onset of the childhood component of growth, growth failure during childhood and fail to undergo a pubertal growth spurt. The magnitude of their growth failure is most apparent during adolescence, a period in which most children are striving to “fit in”. By 15 years of age, the average height of an untreated girl with TS is equivalent to that of only a 9.5-year-old girl in the general population. Because bone maturation is generally delayed, most untreated girls with TS grow slowly into their early 20s, achieving an adult height about 20 cm shorter than their target height [2,6].

2.2. Major genetic determinant of growth failure and skeletal abnormalities

Much of the deficit in height is caused by haploinsufficiency of the short-stature homeobox-containing gene (SHOX) located within the pseudoautosomal region of the X chromosome [7,8]. The SHOX gene belongs to a family of transcriptional regulators, homeobox genes that are major controllers of developmental processes. SHOX mRNA and protein are found in all zones of fetal and childhood growth plates [9].

2.3. Other skeletal abnormalities

Skeletal abnormalities are not restricted to linear growth. Disproportionate growth causes most girls with TS to appear stocky, with a wide body and relatively large hands and feet [10]. SHOX localization to the elbow, knee and wrist during embryonic development is consistent with the increased prevalence of cubitus valgus, genu valgum and short fourth metacarpals in girls with TS. SHOX localization in the first and second pharyngeal arches are consistent with abnormalities in facial development, including a high palate and micrognathia [11,12].

Girls with TS are at higher risk for congenital hip dislocation, patellar dislocation, scoliosis and kyphosis than the general population. Scoliosis (lateral curvature $>10^\circ$) develops in 10–20% of girls with TS, and unlike that in the general population, often begins in early childhood [13,14]. Excessive kyphosis (A–P curvature $>40^\circ$) and/or vertebral wedging (an A–P deformity $>5^\circ$ at an individual vertebral body) is correlated with advancing childhood age and has been reported in 40% of girls ages 5–18 years [13–15].

3. Growth hormone therapy

3.1. Goals of therapy

The goals of growth-promoting therapies are to attain a normal height for age as early as possible, progress through puberty at a normal age and attain a normal adult height. These

goals should be accomplished with the least risk and expense possible. For TS, the centerpiece of growth-promoting therapy is GH, which increases growth velocity and final adult stature.

3.2. *Clinic studies of GH treatment in TS*

During the past two decades, multiple studies have demonstrated the effectiveness of GH treatment in improving final adult stature [16–22]. However, the magnitude of the benefit has typically been calculated using the growth data of historical controls and has varied greatly depending upon study design and treatment parameters [23]. In 2005, the first randomized controlled trial to follow GH-treated TS subjects to final height [24] was published by the Canadian Growth Hormone Advisory Committee, and corroborated the increases in adult stature that other studies had reported. In the Canadian study, 154 girls with TS (aged 7–13 years) were randomly assigned to receive GH (0.3 mg/kg/week, maximum weekly dose 15 mg) or no treatment. GH was continued until height velocity was less than 2 cm/year and bone age was greater than 14 years. Beginning at age 13, all girls with ovarian failure received oral ethinyl estradiol and were cycled with medroxyprogesterone acetate after 2 years. After a mean follow up period of 5.7 ± 1.6 years, the GH group achieved a final adult stature 7.2 cm taller than the control group [24].

3.3. *Variables affecting GH efficacy*

Many factors are known to determine the effectiveness of GH therapy. These include age at initiation of GH therapy, duration of GH therapy, the GH dose, timing of GH administration and, of course, individual patient characteristics such as height and weight. Prediction models built from the data of large GH post-marketing surveillance populations or clinical trials have helped to establish the relative importance of these variables. The factors most important in determining a positive impact of GH therapy on final adult stature are a young age at initiation of therapy [20–22], a long duration of therapy [20,25], a high GH dose [21,26,27] and daily GH administration [25,28].

3.3.1. *Age at initiation of GH therapy*

Age at initiation of GH therapy appears to be the most important factor in determining GH efficacy. GH therapy has traditionally been initiated in mid- to late-childhood when the patient is already 2–3 S.D. below the mean in height. There is a general consensus now that GH should be initiated at a younger age, but exactly how young has not been determined. It is known that growth failure in TS begins in utero and continues at a rapid pace postnatally [3–6]. Therefore, a study was designed to determine if GH therapy would prevent progressive growth failure in infants and toddlers with TS. Preliminary data from the Toddler Turner Study, in which 88 girls between the ages of 9 months and 4 years of age (mean age 2.0 years) were randomized to GH or no GH therapy, indicate that it is safe and effective beginning as early as 9 months of age [29]. After 2 years of treatment, girls in the GH arm gained 1.0 S.D. in height while those in the control group lost 0.6 SD, for a difference of 1.6 S.D. between the two groups.

3.3.2. Duration of GH therapy

Mathematical modeling of the factors associated with adult height in a French population of 704 girls with TS found it difficult to separate the effect of age at initiation of therapy and duration of therapy [25]. However, these two factors together accounted for 66% of the outcome variance and the influence of age was roughly twice as great as the influence of treatment duration.

3.3.3. GH dose

GH therapy in the United States is generally initiated at the FDA-approved dose of 0.375 mg/kg·week (0.054 mg/kg·day=0.162 IU/kg·day=4.8 IU/m²·day). There is a logarithmic effect of GH dose on height; thus, the magnitude of the GH effect diminishes as the dose of GH becomes higher. Nonetheless, up to a certain point, doses higher than those approved by the FDA produce a greater gain in final height with no apparent increase in short-term adverse events [30]. For example, in a study by the Dutch Working Group [17], the mean gain in final height (FH–mPAH) in groups treated with 4 IU/m²·day, 6 IU/m²·day and 8 IU/m²·day averaged 11.9±3.6 cm, 15.7±3.5 cm and 16.9±5.2 cm, respectively.

When GH was given at the higher doses, the levels of IGF-I were often above the normal range [17]. These levels decreased after GH therapy was stopped. The long-term consequences of supraphysiological concentrations of insulin-like growth factor I are unknown [31].

3.3.4. Frequency of GH dose

It is suggested that GH be administered daily at bedtime. Clinical trials in GH-deficient children demonstrated a decade ago that the same weekly dose of GH is more effective when administered daily than three times a week [32]. More recently, independent mathematical models of GH effect in TS have demonstrated that GH is more effective when given seven times than six times a week [25,28]. Administration at bedtime provides more physiologic GH profiles than morning injections [33].

3.4. Other skeletal effects of GH therapy

GH therapy affects other skeletal attributes beyond linear growth and height.

3.4.1. Body proportions

Untreated girls with TS have relatively large trunks, hands and feet, and broad shoulders and pelvis compared to height. In the Dutch Turner dose–response study, the height gain after GH therapy was accompanied by an increase in all measured parameters of body proportions relative to baseline [34]. The disproportion between standing height and sitting height improved moderately during GH treatment. However, the increase in height was accompanied by an even greater increase in the size of the feet. It was concluded that the disproportionate growth of feet observed during GH therapy may be part of the natural development of TS [10], but might be influenced by higher doses of GH.

3.4.2. Bone density

While bone density during childhood has been reported to be normal [35,36], untreated adults with TS have low bone mass, which is associated with an increased risk for fractures, especially osteoporotic fractures, in older women [37]. Appropriate therapy with GH and estrogens improves and may normalize bone mineral density in TS [35,36].

3.5. Safety of GH therapy

GH has had a good safety record [38]. Insulin resistance and carbohydrate intolerance have been reported in untreated girls with TS. Furthermore, GH at supraphysiological doses is associated with a decrease in glucose sensitivity. In the Dutch Turner dose–response study, long-term treatment with GH at doses of up to 0.09 mg/kg/day in girls with TS had no adverse effects on insulin levels [39]. After discontinuation of GH the increased fasting and stimulated insulin levels returned to normal. Similarly, fasting glucose levels increased during GH treatment and decreased after discontinuation of GH treatment, while stimulated glucose levels showed no change during GH treatment.

Girls with TS are also predisposed to develop cardiovascular disease (CVD). It has even been reported that CVD is the main cause of their reduced life expectancy [40]. Risk factors for CVD, including insulin resistance, hypertension and hyperlipidemia occur more frequently in females with TS than in the normal population [41,42]. Long-term GH therapy does not appear to be associated with left ventricular hypertrophy [43] or worsening of the pre-existing relatively high blood pressure in TS, even at higher GH doses [39]. No evidence of dyslipidemia was found after long-term GH treatment [39].

As one would anticipate, GH-induced accelerated growth has been associated with slipped capital femoral epiphysis and worsening of scoliosis. No increased tumor risk has been found, but concern that tumor risk might be increased decades after therapy, remains. A rare, but serious complication of GH therapy is pseudotumor cerebri [38].

4. Adjunctive hormonal therapies

4.1. Oxandrolone

Oxandrolone, a nonaromatizable, anabolic steroid, may be used in combination with GH to augment growth [16,44–47]. When used alone, anabolic steroids increase short-term growth velocity, but do not appear to improve final height [48,49].

4.2. Estrogens

Current data indicate that there is no role for estrogen as a growth-promoting agent. Estrogens, candidates for growth augmentation at one time, do not increase final height, even when given at relatively low doses (ethinyl estradiol 100 ng/kg/day) [21].

5. Recommendations for GH therapy

GH therapy should be directed by a pediatric endocrinologist. The child should be monitored at intervals of 3–6 months. Lengths and heights [1,6,50] of girls with TS on or off GH therapy should be evaluated using TS-specific growth curves. Where possible, these should be specific to ethnic groups and/or nationalities.

GH is used as a pharmacologic agent to enhance growth in girls with TS, not as a hormonal replacement therapy. Provocative GH testing prior to initiation of GH therapy should only be performed in those whose growth is clearly abnormal relative to that expected for TS since girls with TS generally have a normal GH secretory pattern.

Prior to initiation of GH therapy, the family should be given realistic expectations of its efficacy and made aware of potential risks and side effects.

Treatment with GH should begin as soon as growth failure is demonstrated, even in infancy. Initiation of therapy at a young age, optimally while the child is still at a normal length/height, should not only improve outcome but decrease overall cost. It is also likely that the psychosocial benefits of being closer to peers in height throughout life are greater than increasing relative height during late childhood or adolescence. Puberty is more likely to be initiated at a normal age [22] and GH therapy is likely to be terminated earlier.

Treatment should begin with 0.375 mg GH/week divided into daily doses and administered in the evening. The dose can be adapted according to the patient's growth response and IGF-I levels. For the younger child, one strategy would be to titrate the GH dose to achieve IGF-I levels in the upper range of normal [51–53]. Growth prediction models may be helpful in determining the potential effects of changes in dosing [28,54].

Evaluation for scoliosis and kyphosis should be part of the regular physical examination. If present, one may continue GH therapy in close collaboration with an orthopedic surgeon if the curvature can be stabilized by a brace or if surgery will be necessary regardless of the rapidity of growth. Because of the difficulty in the clinical assessment of kyphosis, it has been suggested that spine films be obtained at 2–3-year intervals.

For girls older than 9 years of age or those with extreme short stature, consideration can be given to adding a nonaromatizable steroid, such as oxandrolone. Because oxandrolone is not aromatized into estrogen, its effect on bone maturation is minimal compared to that of other testosterone and other androgens. The dose of oxandrolone should be 0.05 mg/kg·day or less. Higher doses are likely to result in virilization (clitoral enlargement, acne, lowering of the voice, etc.) and more rapid skeletal maturation [55].

For girls who begin GH therapy early, initiation of estrogen replacement therapy using low doses of transdermal estradiol (most physiological) or oral estradiol at a relatively normal age (12 years) is encouraged. This should not compromise final adult stature and is likely to improve quality of life during adolescence [17,56,57].

Recently, health-related quality of life (HRQoL) in young women with TS after long-term growth hormone (GH) therapy and induced puberty was evaluated [58]. A normal HRQoL was found with relative high scores on some of the HRQoL-scales, which can be explained by an estrogen-effect or by a possible response shift, indicating that the TS women might have a different internal reference. Additionally, satisfaction with height and with breast development had a significant positive influence on several HRQoL scales, including social functioning and physical functioning. Therefore, it was hypothesized that

GH and age-appropriate estrogen treatment positively influenced HRQoL in young women with TS. Normal HRQoL was also found in young adults with TS treated with GH in the French population-based cohort study; however, scores were unaffected by height [59].

GH therapy should be continued until a satisfactory height has been attained or until little growth potential remains (bone age >14 years and growth velocity <2 cm/year).

6. Conclusion

A normal height is now an achievable goal for most patients with TS diagnosed and treated with GH beginning in early childhood.

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