Clinical Experience

Issue 24/2011

Growth Hormone therapy in Turner's syndrome

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Introduction

Turner's syndrome (45, X0 karyotype) represents one of the most frequent chromosomal disorders that occur as a result of a complete or partial X-chromosome monosomy, with or without cell line mosaicism, in phenotypic females. The syndrome is characterized by endogenous estrogen deficiency secondary to ovarian dysgenesis and short stature, and is associated with characteristic clinical features; short stature and gonadal dysgenesis are the most consistent clinical features found in Turner's syndrome. The extent of the genes lost in the 2nd X chromosome appears to be dependent factors for the characteristic clinical features.

While many Turner's syndrome girls are diagnosed in mid-childhood while being investigated for their short stature, in other instances, as in the case given below, the condition is diagnosed in adolescence when the girls fail to enter puberty or in adulthood while being investigated for recurrent pregnancy loss. In these cases, levels of growth hormone (GH) are only modestly low except in puberty when there is a lack of estrogen induced augumentation. Consequently, the cumulative GH lack and skeletal resistance to the effects of GH reflects short stature. All individuals with suspected Turner's syndrome are recommended to have a standard 30-cell peripheral blood karyotype.

Case Report

A fourteen year old female child presented to the specialty clinic for evaluation of her short stature and delayed puberty. She had a height of 138 cm and her body mass index (BMI) was 25.4 kg/m^2. Her parents pointed out that they, themselves, were of normal stature (father, 180 cm; mother, 162 cm). The breast development of the patient was at stage 1, and her pubic hair development was at stage 1-2 consistent with the Tanner's staging system for puberty. She had a bone age corresponding to that of a girl aged 12-13 years.

Following characteristic features were found to be present on her physical examination: epicanthus; micrognathia; shield chest; short webbed neck; cubitus valgus; short 3rd and 4th metacarpals and metatarsals.

No pigmented nevi were seen on her face and body. After noticing a low-pitched systolic murmur on auscultation, an echocardiography was subsequently performed revealing coarctation of the aorta that was hemodynamically non-significant, with normal blood pressure in both arms, and normal aortic root diameter, and no

evidence of valvular abnormalities. A normal kidney and a prepubertal uterus were revealed on ultrasound abdomen; while the ovaries could not be visualized. Investigations revealed increased plasma levels of follicle-stimulating hormone (FSH; 113.2 mIU/ml) and luteinizing hormone (LH; 22.9 mIU/ml). Considering the patient's clinical features, a standard 30 cell karyotype analysis was performed, which confirmed the diagnosis of Turner's syndrome revealing a 45X karyotype with no evidence of mosaicism. The projected adult height was estimated to be 148 cm.

A decision was made to start GH therapy, and she was started on a GH dose of 2 IU/kg/day. Also, she was prescribed estrogen therapy considering her relatively advanced chronological age, and her wish to start puberty. She received 0.005 mg (5 µg) Ethinyl estradiol during the first three months that was gradually increased to 10 µg, 15 µg and 20 µg at 3 monthly interval. She had breakthrough bleeding about one year later, and was prescribed 25.0 µg/day Ethinyl estradiol along with medroxy progesterone. An increase of 10 cm was noted in the patient's height, and she reached a final height of 148 cm on the above described growth-promoting therapy. About one year later, GH was withdrawn since the patient's epiphyses had fused by that time. She reached pubertal stage 3 of Tanner's classification and continued her hormone replacement therapy (HRT). The patient appeared satisfied with her height. Also, she appreciated the fact that she had entered puberty.

Discussion

GH therapy, effective in increasing final adult height, accelerates growth in patients with Turner's syndrome; earlier onset of treatment and higher doses gives better outcomes.[1] However, despite a characteristic phenotype, several Turner's syndrome patients may not be diagnosed, and may in fact have a late diagnosis. About 22% of Turner's syndrome girls are diagnosed after the age of 12 years as shown by the Belgian Study Group data, most of them with large height deficit.[2] These patients, like the case mentioned above, have missed the opportunity of earlier GH treatment that could have lead to normalization of the height during childhood. Also, they have missed the opportunity of an age-appropriate puberty induction.

An early diagnosis of Turner's syndrome has potential advantages. Evidence based on a randomized, controlled trial, GH supplementation in girls with short stature due to Turner's syndrome, with induction of puberty at a near physiological age, increases the adult height of Turner's syndrome girls.[3] While the optimal age for initiating GH treatment in patients with Turner's syndrome has not been established, it is recommended that treatment should be considered as soon as growth failure (decreasing height percentiles on a standard growth curve) is demonstrated. In general, GH therapy is recommended to be initiated at a weekly dose of 0.375 mg/kg; it is very effective when given daily and administered in the evening.

Subsequent dosing can then be adapted consistent with the patient's growth response and their serum levels of insulin-like growth factor I (IGF I).[4] Higher doses of GH should be considered in girls > 9 years of age, or in those with an extremely short stature.[4,5] The growth promoting therapy may be continued until attaining a satisfactory height, or until little growth potential remains.

An absence of pubertal development is one of the most common features seen in patients with Turner's syndrome. Ultimately, most of the patients have gonadal failure, as presented in the case above. It is recommended that the levels of serum gonadotropin should be measured before initiating the estrogen therapy in order to exclude the possibility of delayed spontaneous pubertal development. While therapy with low dose estradiol can be initiated as early as 12 years of age,[4] this is possible only if the syndrome is diagnosed early enough. Considering the individuals desire to begin puberty, the dosing and timing of estrogen therapy, meant for inducing pubertal development, should probably aim at mimicking the normal pubertal development.[6] Height SDS as a continuous variable is the most effective measure of growth when considering pretreatment factors that may influence response to GH therapy.[7] Usually, replacement therapy is begun at 1/8th to 1/10th of the adult replacement dose, and then gradually increased over 2-4 years. In general, estrogen replacement therapy is required until there is normal menopause in order to maintain feminization, and to prevent osteoporosis. Progestin addition is advised to be delayed for at least two years after starting estrogen therapy, or until there is breakthrough bleeding, in order to allow for normal breast and uterine development.[4] Since the syndrome, and its treatment, might affect the patient's sexual development and function, and also her reproductive potential, it appears important to engage the patient in a discussion regarding this.

In Turner's syndrome patients, transition from pediatric to adult healthcare is an important management issue and should occur at the completion of growth and puberty, during late stage adolescence.

Summary

Turner's syndrome should be considered in girls with an unexplained short stature and/

or with primary or secondary amenorrhea, and a cytogenetic analysis should be performed, even in absence of other obvious abnormalities associated with Turner's syndrome.

The dose of the GH and the duration of therapy are important for favorable height outcomes, and the growth promoting therapy may be continued until attaining a satisfactory height, or until little growth potential remains; there is greater height gain with longer treatment with GH.[5] In addition to promoting linear growth, GH also has favorable physiologic effects on adipose tissue, bone metabolism, and muscle accretion.[8] It directly stimulates osteoblast and osteoclast differentiation, and promotes accretion of bone mass during childhood and adolescence.

Together with growth issues, it is also important to consider the patient's desire to begin puberty in order to establish an optimal hormonal treatment plan. The dose and timing of the hormonal therapy in Turner's syndrome patients should reflect the process of normal puberty, and should not interfere with the positive effect of GH treatment on the patients' final adult height.

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