

Turner Syndrome: A Genetic Cause of Short Stature

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Turner syndrome (TS) occurs approximately one in 2000-2500 live born females and manifest with various clinical features, such as growth failure, pubertal delay/ovarian failure, cardiac anomalies, ear and eye problems and osteoporosis. Besides renal abnormalities, autoimmune diseases and obesity/ metabolic disorders are other features. 25% of patients are diagnosed late in adult period. Foot edema at birth, ptosis, descent in neck hair, cubitus valgus are the common symptoms of Turner girls. Most girls and women with Turner syndrome have normal intelligence. Developmental delays, nonverbal learning disabilities and behavioral problems are possible, although these characteristics vary among affected individuals [1,2].

The most common feature of Turner syndrome is short stature, which becomes evident by about age 5. An early loss of ovarian function (ovarian hypofunction or premature ovarian failure) is also very common. The ovaries develop normally at first but egg cells (oocytes) usually die prematurely and most ovarian tissue degenerates before birth. Many affected girls do not undergo puberty unless they receive hormone therapy and most are unable to conceive (infertile). A small percentage of females with Turner syndrome retain normal ovarian function through young adulthood [1].

Mostly encountered chromosomal abnormality is 45X0 (about 50%) and other chromosomal abnormalities are seen in table 1.

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| <ul style="list-style-type: none"> • 45 X0 • Deletion in short or long arms of chromosome X • Ring formation • Duplication in long arm of chromosome X • Mosaicism (45X/46XX, 45X/46XY, 45X/47XXX) |
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Table 1: Genotype in Turner syndrome.

The main features of girls with TS is short stature which is thought to be due to typical growth pattern; a mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, growth failure during childhood, and the absence of a pubertal growth spurt [1-3].

Although growth hormone (GH) levels are normal in TS patients, much of the deficit in height is caused by haploinsufficiency of the short stature homeobox containing gene (SHOX) located within the Xp-terminal, pseudoautosomal region of the X chromosome. It affects virtually all individuals with TS and results in an average adult stature 20 cm shorter than their target height with about 143 - 144 cm. Taking account this fact, a higher dose GH is initiated for growth promoting therapy in these patients. A Turkish cohort of 842 patients showed that paternal height plays a major role in linear growth at all ages of TS. TS patients having shorter parents are at increased risk of short stature. No relations were found with birth length and weight and chromosomal disorder type with the degree of short stature [3,4].

Adults with TS have increased IGF binding protein 3 proteolytic activity and low IGF1 but are generally not GH deficient. In a controlled, randomized study to adult height, patients with TS gained 7.3 cm over a mean of 5.7 year of treatment with GH, even using doses slightly lower than those approved today in both Europe and US [5].

Studies show that besides height increment, GH therapy improves body proportions and may contribute to lower diastolic blood pressure in TS. Similar beneficial effects have been seen in relation to total cholesterol, low density lipoprotein, high density lipoprotein showing less obesity and better glucose tolerance without bone age advancement [1].

GH response to treatment in TS is related with the age, dosage, duration of treatment and the height of the child at the commencement of therapy. It is recommended to start at earlier ages to get better response so advised to talk to the parents about GH therapy at the time when the growth curve begins to decline. Recognizing that 90% of young girls with a 45X karyotype will fall below the 5th percentile in height by the age of 5 years, GH is warranted as soon as growth failure becomes evident.

Food and Drug Administration of USA (FDA) approved 0.375 mg/kg/week (0.053 mg/kg/daily) GH dosage has produced additional gains in adult height but higher doses correlate with high IGF1 levels [1,2,6,7]. Because both slipped capital femoral epiphysis and idiopathic intracranial hypertension (with some cases of persistent visual deficits) have been reported with GH treatment in TS and appear to occur at a higher rate compared with the treatment of GH deficiency or idiopathic short stature, further attempts to increase GH dosage appear unwarranted. Monitoring with IGF1 and height velocity response to treatment can be used to adjust dosing [6-8].

Treatment should be stopped when little growth potential remains (bone age > 14 or growth velocity < 2 cm/year).

40% of mosaic Turners, 8 - 30% of 45 X0 cases could show spontaneous puberty but in 90% of this puberty do not progress. So, most of them need pubertal induction and long term estrogen therapy. Patients could be started on low dose ethinyl estradiol as early as 5 years of age (mean age 9.3 years) as opposed to beginning by age 12, as is generally done today [1,2]. Earlier treatment could make positive effects on bone mineral density and uterine development but generally beginning dose could be correlated with commencement of GH treatment, if GH treatment began before age 8 begin estrogen at 12; if GH treatment began between 8 - 11 begin estrogen at 13 - 14 years; if GH began after 11 years than begin estrogen treatment after 2 years of GH treatment or at age 15. Estrogen treatment should begin with 1/6 - 1/4 of adult dose and the increments should be done in 3 - 6 months and in 2 - 4 years should reach adult dose. Adult dose is 0.1 mg/daily for transdermal estrogen, 20 mg/daily for ethinyl estradiol and 1.25 mg/daily for conjugated estrogen [1,2].

Scoliosis and kyphosis occur in 10 - 20% of girls with TS most commonly in adolescence and reported more commonly with GH therapy, so careful monitoring for scoliosis is warranted [9].

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