

Strategies to Prevent Delayed Diagnosis in Turner Syndrome

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Turner Syndrome occurs in about 1:2000 live female births.¹ It is characterized by the absence of all or part of the normal second sex chromosome, and presents with a constellation of physical findings that often includes congenital lymphedema (puffy hands and feet), short stature, and gonadal dysgenesis.

Diagnosis

Puffy hands and feet (congenital lymphedema) alerts one to the diagnosis of Turner Syndrome in about one quarter of affected girls.² Some infant girls may have webbed neck. Occasionally, infants receive the diagnosis because of the presence of coarctation of the aorta. However, many girls with TS do not have any obvious stigmata. One third of girls with Turner Syndrome are diagnosed in midchildhood on investigation of short stature. Most of the remainder of females with Turner Syndrome are diagnosed in adolescence when they fail to have normal pubertal breast development and/or fail to have initiation of menses. Rarely, the diagnosis is not made until adulthood, because of recurrent pregnancy loss.

Typically, the diagnosis is confirmed by standard cytogenetic analysis (karyotype). There are faster and less expensive methods for diagnosing TS, using the detection of single nucleotide polymorphisms (SNPs) on the X chromosome.³ Approximately half of the karyotypes in females with TS reveal a single X chromosome (45, X) in all cell lines. Others have mosaicism, meaning that they have an additional cell lineages besides 45,X. It is important to know the exact cell lines present, since girls with mosaicism for a cell population with a Y chromosome are at increased risk for malignancy (gonadoblastoma) in the streak gonads.⁴

Manifestations and Management

Short Stature

Women with Turner Syndrome reach an adult height 20 cm below their expected midparental height.⁵ The mean final adult height is about 143 cm, which is about 4 feet, 8 inches.⁵ At birth, the length tends to be close to the normal range. However, by 18 months of age, many girls with Turner Syndrome will have a decrease in their growth velocity. Approximately 2% of girls whose height is below the 5th percentile have a diagnosis of Turner Syndrome. It is important to point out that children with Turner

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Syndrome may not be very short; however, they will be shorter than expected for their midparental target height.

Treatment with recombinant human growth hormone is now the standard of care for girls with Turner Syndrome. Data reported from the National Cooperative Growth Study (NCGS) indicate that from 1995 to 2000, girls with Turner Syndrome were not started on growth hormone until an average age of 9.0 ± 3.8 years. Furthermore, their height at initiation of growth hormone therapy was -2.9 ± 0.9 SDS, which is approximately the 0.1%.⁶ This delay in starting growth hormone therapy is likely related to delayed diagnosis of Turner Syndrome in some girls, and in others it is due to delay in referral to a pediatric endocrinologist. The later growth hormone therapy is started, the longer it will take for the girl's height to improve to the normal range, and the less likely they are to reach a final adult height within the normal range.

A recent randomized controlled trial evaluated the effect of early growth hormone therapy in the toddler years in girls with Turner Syndrome. During this two year study, the control group had progressive growth failure, with a decrease in height from -1.8 ± 1.1 SDS (at baseline) to -2.2 ± 1.2 SDS (after 2 years). This is in contrast to the growth hormone treated girls, whose mean height score increased from -1.4 ± 1.0 SDS (at baseline) to -0.3 ± 1.1 SDS (after 2 years).⁷ This means that after 2 years, the untreated girls were at about the 1% and the growth hormone treated girls were at about the 40%.

Gonadal Failure

The ovarian cells in females with Turner Syndrome undergo premature cell death. By 20 weeks gestation, 70% of ovarian germ cells were apoptotic in those with Turner Syndrome, compared to 3% in age-matched normal XX ovaries.⁸ The ovarian failure manifests itself as both estrogen deficiency as well as a lack of fertilizable ovum.

Girls with Turner Syndrome tend to have normal pubic and axillary hair development, as these are due to adrenal androgens, rather than ovarian estrogens. However, most girls with TS will not have full breast development nor menstrual cycles. Occasionally, there is enough residual ovarian function for breast development and/or menstrual periods. Because of the ovarian failure, natural fertilization is quite rare in women with TS.

The estrogen deficiency is treated with replacement estrogen, either as pills or estrogen patches. Studies show that estrogen patches have the advantage of not causing liver enzyme elevations⁹ and promote increased growth factor (IGF-1) levels.¹⁰ There are various estrogen replacement regimens that are used, but the common point among of all

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of them is to start with low dose estrogen, and slowly increase the dose over a couple of years. This allows for normal uterine and breast development.

There is much research looking into various forms of assisted reproductive technologies to help women with TS carry a pregnancy. There have been reports of ovarian tissue wedge freezing as well oocyte cryopreservation in young women with Turner Syndrome, in order to preserve fertility.¹¹

Developmental and Learning Issues

In general, most people with TS have normal intelligence. Some of the deficits that are more common in females with TS include: visuospatial organization, social cognition, and math abilities. Attention deficit disorders are also more common in these individuals.² As with anyone with learning disabilities, early diagnosis and interventions are very important.

Cardiovascular Issues

Approximately one quarter to one half of all females with TS have congenital heart disease. Therefore, all individuals with TS should at least have an echocardiogram at the time of the diagnosis of TS. Typically the malformations are left-sided defects, with coarctation of the aorta and bicuspid aortic valve being the most common. There seems to be an increased risk of aortic root dilatation and subsequent aortic aneurysms in individuals with TS.¹²

Endocrine Issues

Acquired hypothyroidism is more common in females with TS. Approximately, 41% of women with TS have anti-thyroid antibodies, with about one-third of these women having hypothyroidism, requiring thyroid replacement. Interestingly, 83% of the women with the particular karyotype, X-isochromosome, have anti-thyroid antibodies. The hypothyroidism tends to occur in the 20s and the 30s, but a few percent of cases present in early childhood.¹³

Some studies have found an increased incidence of obesity, insulin resistance, and type 2 diabetes in women with TS.²

Otological Concerns

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Recurrent ear infections are quite common in females with TS. By a mean age of 2 years, over 50% of girls already had a history of recurrent otitis media.¹⁴ This increased incidence of infection is due to a shorter, more horizontal eustachian tube, interfering with middle ear drainage and causing nasopharyngeal reflux.

Approximately, one-quarter of girls with TS with have hearing loss, typically conductive hearing loss related to the middle ear dysfunction and chronic ear infections. However, sensorineural hearing loss is also more common in females with TS.¹⁴

Renal Concerns

Approximately, one third of females with TS have kidney malformations.¹⁵ These anomalies include: horseshoe kidney, single kidney, duplicated collecting system, and pelvic kidney. Therefore, a renal ultrasound is recommended at the time of diagnosis of TS.¹⁵

Musculoskeletal and Orthopedic Concerns

Commonly, increased carrying angle of the arm is found, due to malformation of the ulnar head. Congenital dislocation of the hip and scoliosis tend to be more common in girls with TS. Other malformations that occur in TS are: webbed neck, widely spaced nipples, nail dysplasia, high arched palate, and short forth metacarpal.

Dermatological Concerns

The congenital edema of the hands and feet tend to resolve on their own within the first couple years of life. Nevi tend to be more common in females with TS. There also seems to be an increased incidence of keloid formation in these individuals.

Strategies to Prevent Delayed Diagnosis

One study found that girls with TS were not diagnosed until an average of five years from the time that their height fell below the 5th percentile.¹⁶ The authors of that study proposed the following guidelines for screening for TS: Any girl with one or more of the following: Short stature (height <5th percentile), webbed neck, peripheral lymphedema, coarctation of the aorta, or delayed puberty, should be screened for TS. Additionally, any girl who has at least two or more of the following: nail dysplasia, high arched palate, short fourth metacarpal, and strabismus, should be screened for TS.¹⁶

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