

Review article

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Diagnostic and therapeutic considerations in Turner syndrome

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Newly developed genetic techniques can reveal mosaicism in individuals diagnosed with monosomy X. Noninvasive prenatal diagnosis using maternal blood can detect most fetuses with X chromosome abnormalities. Low-dose and ultralow-dose estrogen replacement therapy can achieve a more physiological endocrine milieu. However, many complicated and controversial issues with such treatment remain. Therefore, lifetime observation, long-term studies of health problems, and optimal therapeutic plans are needed for women with Turner syndrome. In this review, we discuss several diagnostic trials using recently developed genetic techniques and studies of physiological hormone replacement treatment over the last 5 years.

Keywords: Turner syndrome, Diagnosis, Hormone replacement therapy

Introduction

Six cases of a syndrome of infantilism, congenital webbed neck, and cubitus valgus were first reported by Turner in 1938. There was a definite genital change in 2 cases following administration of anterior pituitary gonadotropic hormone¹. Around 20 years later, this so-called Turner syndrome (TS) was identified as X chromosome monosomy². The phenotype of this syndrome was described as follows: short stature, broad chest, congenital lymphedema, low posterior hairline, prominent ears, narrow and acutely arched palate, abnormal fingernails, lack of pubertal onset by adolescence, presence of streak ovaries, normal intelligence³. The most common ages at which females present with TS include the newborn period, when they present with lymphedema or cardiac anomalies; school age, when they present with short stature; and adolescence, when they present with a lack of pubertal onset.

Recently developed genetic techniques can reveal mosaicism in individuals diagnosed with monosomy X. Additionally, noninvasive prenatal diagnosis using maternal blood can detect most cases of X chromosome abnormalities⁴. This review included diagnostic issues and hormone replacement therapy as therapeutic issues. We firstly introduced several diagnostic trials using newly developed genetic techniques. Then, we reviewed recent studies on hormone replacement therapy for optimal growth and puberty for patients with TS from the last 5 years. The fertility issue, neurocognitive issue, cardiovascular health issues, and health surveillance for comorbidities throughout the lifespan were not included in this review.

Diagnostic considerations

1. Genotype and phenotype

The birth incidence of TS is 1 in 2,000–2,500 live-born girls. Monosomy X underlies 50% of cases, and the others have mosaicism. There is a known poor genotype-phenotype correlation in TS⁵⁻⁷. This may be due to heterogeneity in tissue mosaicism, which also makes TS difficult to diagnose. When the length and weight of neonates with TS are compared among different

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karyotypes at birth, there is no effect of karyotype on height in girls with TS, whereas weight is greater in girls with 46,X,i(Xq) and 45,X/46,X,i(Xq) karyotypes⁸⁾. For early diagnosis, population-based, validated cutoff values for height-for-age, height distance from target height, and changes in growth rate were suggested, with 97% sensitivity and 96% specificity in all girls with TS. However, this method is so complicated that computerized analysis is required for practical use⁹⁾. Short-arm X chromosome deletion causes many phenotypes, whereas long-arm deletion, particularly the loss of Xq26–Xq28, is significantly related to abnormal ovarian function without characteristic Turner features¹⁰⁾.

2. Noninvasive prenatal test

Whole-genome sequencing of circulating cell-free DNA in maternal plasma has enabled noninvasive prenatal testing for common autosomal aneuploidies, including TS (45,X). However, the incidence of mosaicism may complicate noninvasive prenatal testing, particularly with respect to gonadal dysgenesis in the adult female population. In one study, the combined sensitivity for detecting sex chromosome aneuploidies was 96.2%, the false positive rate was 0.3%, and the nonreportable rate was 5%¹¹⁾. In another report, which excluded mosaic samples, the results corresponded to a sensitivity of 100% and a specificity of 99.75% for detecting sex chromosome aneuploidies¹²⁾. This method may miss structurally abnormal X chromosome and mosaicism.

3. Real-time polymerase chain reaction

Real-time polymerase chain reaction (PCR) gene quantification can be used for diagnosis of TS^{13,14)}. Correa et al.¹⁴⁾ proposed an algorithm for neonatal TS detection using 2 study genes and one normalizing gene, *ARSE* (arylsulfatase E-OMIM 300180), *MAGEH1* (melanoma antigen, H1-OMIM protein: 300548), and *HBB* (beta hemoglobin, OMIM OMIM 141900), which are located in the telomeric pseudoautosomal region (*ARSE*-Xp22.3), the pericentromeric region (*MAGEH1*-Xp11.21), and on the autosomal chromosome (*HBB*-11p15.5), respectively. *ARSE/HBB* and *MAGEH1/HBB* ratios less than 0.81 and 1.24, respectively, confirm a diagnosis of TS.

4. Single nucleotide polymorphism arrays

Single nucleotide polymorphism (SNP) array genotyping can provide superior resolution in comparison to metaphase karyotype analysis. Cytogenetic analysis by karyotyping is too labor intensive for rapid population-based screening and may fail to detect small fragments of Y chromosome material. Prakash et al.¹⁵⁾ showed that SNP array genotyping is a feasible alternative to karyotype testing in diagnosing TS, particularly for detecting cryptic Y chromosomes. However, using arrays led to incorrect interpretation of rare cell lines that were present in

fewer than 5% of sampled cells. Additionally, karyotyping retains an important advantage over arrays for identifying complex mosaicism, including translocations and rare X chromosome structural variants. SNP genotyping is incapable of detecting fully balanced X chromosome translocations.

5. Detection for cryptic mosaics

One meta-analysis¹⁶⁾ questioned whether pure monosomy X occurs. Although 45,X, the characteristic karyotype associated with TS, is the only viable monosomy in humans, only around 1% of conceptuses recognized with this karyotype survive until live birth. The authors suggested a "rescue line" as one with a viable karyotype(s), the presence of which enables the survival of a putative nonmosaic aneuploid embryo to live birth. In this regard, they arrived at some hypotheses: that all 45,X individuals with TS are cryptic mosaics, the absence of the X chromosome in 45,X embryos is primarily caused by mitotic factors, and the placenta is a strong candidate for the location of the rescue line in apparently nonmosaic 45,X individuals. More efforts are needed to identify cryptic mosaic 45,X TS patients by counting more cells during karyotype analysis, examining additional tissues, and using SNP microarrays, fluorescence *in situ* hybridization, and PCR methods.

Therapeutic considerations: focus on hormone replacement therapy for growth and puberty

1. Growth hormone

Skeletal disproportion in TS includes the following phenotypes: micrognathia, high-arched palate, short fourth metacarpals, genu valgum, Madelung wrist deformities, and short limbs. Short stature, recognized by Lemli and Smith³⁾ as a ubiquitous abnormality, is now effectively treated with early initiation of recombinant growth hormone (GH) therapy¹⁷⁻¹⁹⁾. Achieving as normal a height as possible through GH therapy has become standard²⁰⁾. Several growth references (including one from the World Health Organization) for TS have been published and reviewed²¹⁻²³⁾. Homeobox-containing gene *SHOX* haploinsufficiency has been well established as causing a wide spectrum of short stature phenotypes in patients with TS²⁴⁾. Other pathophysiological pathways not involving *SHOX* may affect both fetal and postnatal growth, and response to GH in TS²⁵⁾. The sitting height/height standard deviation score tends to improve with age in TS patients, and is inversely correlated with age at puberty onset. This phenomenon may be explained by the low exposure of growth cartilage to estrogens and the relatively late start of exogenous estrogens in most girls with TS, which protects them from early epiphyseal closure and may therefore attenuate body disproportion, allowing for a longer period of limb growth, in comparison to girls with isolated *SHOX* defects²⁶⁾. As short stature in *SHOX* deficiency and TS share a similar etiology, GH replacement therapy shows

similar efficacy in both disorders¹⁸). A large-scale study in Japan showed that GH treatment was effective for increasing the height of children with GH deficiency or TS²⁷. Individual sensitivity to recombinant human GH is known to be variable²⁸. GH induces significant growth acceleration during the first year, but the response wanes over time^{18,19,27}. Specific growth-related genetic markers are associated with growth response in TS^{29,30}. Tyrosine-protein phosphatase nonreceptor type 1 (*PTPNI*; rs2038526) and estrogen receptor alpha (*ESR1*; rs2347887 and rs6927072) were shown to influence height velocity in TS³⁰. Homozygosity for the suppressor of cytokine signaling 2 (*SOCS-2*; rs3782415) T allele, the growth hormone receptor (*GHR*) exon 3 full-length allele, and/or the -202 locus of the insulin-like growth factor binding protein 3 promoter region (rs2854744) C allele were related to a low response to GH replacement therapy in TS³¹. These results suggest that a pharmacogenomic approach of individualized plans for GH replacement therapy should be considered in TS patients. Schrier et al.³² suggested that dosing GH per body surface area (m²) is as efficacious as dosing per body weight (kg), and is more cost-effective. Long-term GH therapy has a positive influence on craniofacial development in TS girls, with the greatest impact on posterior facial height and mandibular ramus³³. A lichen planus-like drug reaction associated with GH therapy was reported in a child patient with TS³⁴.

2. Addition of androgen to GH

To increase adult height, nonaromatizable androgens such as oxandrolone and stanozolol can be used³⁵⁻³⁷. If a patient is severely short for her age, very short adult height is expected, or growth rate is modest despite GH use, additive treatment with the anabolic steroid oxandrolone (0.03–0.05 mg/kg/day, from the age of 10 years or older) can be considered. Possible adverse events such as virilization (e.g., clitoromegaly, voice deepening, hirsutism and acne), delayed breast development, and decreased HDL cholesterol levels, are not commonly reported at dosages of less than 0.06 mg/kg/day³⁶. However, the possibility for the unwanted adverse effects prompts the need for caution in clinical use of androgen³⁸.

3. Sex hormone replacement; estrogen and progesterone

Estrogen replacement therapy (ERT) is required to initiate and maintain pubertal development in women with TS^{17,20}. It is not recommended for girls with spontaneous puberty. Serum anti-Müllerian hormone (AMH) levels are a known sensitive marker of follicular pool in prepubertal girls with TS. A strong relationship was observed between measurable serum AMH and signs of spontaneous puberty, such as breast development and menarche, in TS³⁹. The goal of ERT is to achieve the physiological endocrine milieu at a tempo consistent with the peer group. Since there is no estrogen patch in Korea so far, oral estrogen therapy is used. To mimic peripubertal estradiol levels

(7–24 pmol/L), a starting dose of 50–70 ng/kg/day estradiol is recommended, and for breast development (24–46 pmol/L), 80–120 ng/kg/day is recommended⁴⁰. An ultralow-dose of 25 ng/kg/day ERT beginning as early as 5 years of age was even recommended, because childhood ERT normalized the onset and tempo of puberty⁴¹. However, the recently updated guideline from the 2016 Cincinnati International Turner syndrome meeting recommend that estrogen replacement should start between 11 and 12 years of age increasing to adult dosing over 2–3 years. They suggests to not routinely add very-low-dose estrogen supplementation in the prepubertal years to further promote growth⁴². No differences in body composition, lipid oxidation, or lipid concentrations were observed between transdermal and oral routes of estrogen administration. However, transdermal administration results in a more physiological estrogen milieu than oral administration⁴³. Moreover, oral administration may increase the risk of venous thromboembolism more than the transdermal route⁴⁴. Although individualized dosage protocols may be ideal for puberty induction with low-dose oral estradiol, fixed dosages within a fixed period can be considered to avoid the need to adjust the dose at each visit⁴⁵. A 5-year prospective double-blind randomized controlled clinical trial did not recommend higher estrogen doses in TS girls with increased risk of fractures, because this treatment did not affect bone mineral density or bone markers⁴⁶. Inducing puberty at a physiologically appropriate age in girls with TS is important because it can improve self-esteem, social adjustment, and initiation of sex life⁴⁷. The Pediatric Endocrine Society standardized clinical assessment and management plan algorithm for estrogen replacement may be useful⁴⁸.

Progesterin should be added once breakthrough bleeding occurs, or after 2 years of estrogen treatment⁴², which can reduce the risk of endometrial cancer and/or breast cancer related to prolonged unopposed estrogen, although the risk is low in TS^{49,50}. Progesterin can be added for 10 days each month for withdrawal bleeding, and adult women with TS should preferably continue treatment with estrogen in combination with a sequential progesterone.

Conclusion

There have been marked advances in the diagnosis and treatment of TS since its first description in 1938 by Turner. GH therapy for achieving nearly normal height through and sex hormone replacement therapy for inducing normal pubertal development have become standard therapies. The feasibility of molecular techniques for diagnosis needs to be further established. Since normal height attainment and age-appropriate pubertal development have reported to improve quality of life in young adults with TS^{47,51}, further prospective studies are needed for optimal growth-promoting treatment and puberty-inducing schedule.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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