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Current best practice in the management of Turner syndrome

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Abstract: Turner syndrome (TS) is characterized by partial or complete loss of the second X-chromosome in phenotypic females resulting in a constellation of clinical findings that may include lymphedema, cardiac anomalies, short stature, primary ovarian failure and neurocognitive difficulties. Optimizing health care delivery is important to enable these individuals achieve their full potential. We review the current best practice management recommendations for individuals with TS focusing on the latest consensus opinion in regard to genetic diagnosis, treatment of short stature, estrogen supplementation, addressing psychosocial issues, as well screening for other comorbidities. A multidisciplinary approach and a well-planned transition to adult follow-up care will improve health care delivery significantly for this population.

Keywords: diagnosis, guidelines, screening, Turner syndrome

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Introduction

Turner syndrome (TS) results from the partial or complete loss of the second X-chromosome in phenotypic females and has a prevalence of 1 in 2000 to 2500 live born female children.[1] The initial description by Henry Turner in 1938 included short stature, sexual infantilism, cubitus valgus and pterygium coli.[2] Girls with TS have significant variability in their clinical presentation and especially those with lower degrees of mosaicism for monosomy X may not present with the classic phenotype at all. Short stature, pubertal delay/ovarian insufficiency, cardiac and renal abnormalities, sensorineural hearing loss, ophthalmologic problems, thyroid abnormalities, metabolic syndrome, inflammatory bowel disease and neurocognitive issues are all recognized to be relatively common in TS. Recent diagnostic and therapeutic advances have improved the recognition of these comorbidities and their management. In this review, we present the best practice management guidelines as developed by a recently held international Turner Syndrome Consensus Group meeting.[3] These newer guidelines specifically address the diagnostic screening process and the management of comorbidities in TS. Cardiovascular comorbidity is discussed in great depth including categorization of risk for aortic dissection, and sports participation. The screening and intervention for neuropsychological issues in TS and the importance of transition to adult care are also emphasized.

Diagnosis

The diagnosis of TS can occur at a wide range of ages.[4–6] Prenatally, ultrasound findings of increased nuchal translucency, cystic hygroma, left-sided obstructive cardiac anomalies (especially coarctation of the aorta) in the fetus are highly suggestive of TS.[7] Maternal quadruple serum screening may also be abnormal, but confirmatory testing with amniocentesis or chorionic villous sampling is necessary to entertain the diagnosis of TS prenatally.[4] It is, however, mandatory to repeat the karyotype postnatally in all individuals who were previously diagnosed prenatally.[3,4] Noninvasive prenatal testing using maternal cell-free DNA has not been shown to have a good positive predictive value to diagnose TS and is therefore not recommended for prenatal diagnosis of TS.[8]

Webbed neck, lymphedema or coarctation of the aorta in infancy should prompt a peripheral blood karyotype to rule out TS. While the previous guidelines[4] suggested a peripheral blood karyotype should be considered in girls with unexplained short stature or delayed puberty, or the constellation of characteristic dysmorphic features, the new

guidelines[3] propose the following indications to cover an expanded phenotype:

(a) Karyotyping may be undertaken in the presence of a single clinical feature such as fetal hydrops or cystic hygroma, unexplained short stature, delayed puberty, obstructive left-sided cardiac abnormality (such as a bicuspid aortic valve, coarctation, aortic stenosis, hypoplastic left heart syndrome or mitral valve abnormalities), characteristic facial features (such as short broad neck with webbing, narrow palate, micrognathia, low set ears and down-slanted palpebral fissures with epicanthal folds), or in a couple presenting with infertility.

(b) Karyotyping should also be undertaken if two or more features commonly associated with TS such as renal anomaly (hypoplasia, aplasia or horseshoe kidney), other cardiac anomalies (e.g. partial anomalous pulmonary venous return, atrial or ventricular septal defects), Madelung deformity, dysplastic nails, multiple nevi, neuropsychological issues, and hearing loss associated with short stature are seen in a girl.

The standard 30-cell karyotype is recommended and can detect 10% mosaicism with 95% confidence.[9] Additional tissues or more metaphase spreads may need to be analyzed if there remains a strong suspicion that a patient has TS despite a normal standard karyotype analysis. However, most experts agree that less than 5% mosaicism for X-chromosome haplo-insufficiency probably means that the patient is unlikely to demonstrate features consistent with a TS phenotype. Routine testing with fluorescent *in-situ* hybridization (FISH), chromosomal microarray or karyotype of buccal tissue/skin fibroblasts is not necessary, but may be considered in virilized girls in whom Y-chromosome presence was not demonstrated by a standard karyotype analysis.[10] Multiple sequences adjacent to the Y-centromere should be amplified using polymerase chain reaction (PCR) techniques that are more sensitive than FISH to detect cryptic Y-material.[3,11] When Y-chromosome material is present in the standard karyotype or on such additional testing (incidence of 5–12%), prophylactic gonadectomy is still recommended by expert consensus, albeit at a lower quality of evidence, due to an increased risk (around 10%) of gonadoblastoma.[3]

Several girls have delayed diagnosis in late adolescence or early adulthood with some estimates indicating that up to 38% of TS patients are diagnosed in adulthood.[12] In an update to the previous guidelines, in women over 50 years of age, a new finding of a low level of mosaicism for monosomy X (<5%) does not warrant a diagnosis of TS.[13] Small deletions of the long arm of the X-chromosome distal to Xq24 are also not included in the diagnosis of TS.[3,4] Genotype–phenotype correlations should guide clinical management, but it is now recommended that general surveillance be followed for all TS patients regardless of karyotype.[3]

Short stature

Short stature is the most common finding in TS, seen in nearly all patients and is due to haploinsufficiency of the short stature homeo-box containing gene (SHOX) on the X-chromosome.[14] Growth hormone (GH) secretion is preserved in TS and provocative testing is usually not required. Recombinant GH therapy has been shown to improve adult height in patients with TS by 5–8 cm in several randomized trials and observational studies,[15–19] but the efficacy is variable and depends on multiple factors including mid-parental height, age at initiation of GH therapy, duration and dose of GH therapy and baseline height prior to initiation of GH therapy.[15,19,20] GH therapy is recommended as early as 4–6 years of age or sooner in the presence of growth failure to enable an adequate duration of therapy before pubertal initiation.[3,17] The typical dosing range for GH therapy in the United States (US) is 50–54 μg/kg/day (0.35–0.375 mg/kg/week) and is 45–50 μg/kg/day in Europe (slightly lower in Australasia).[3] The latest guidelines recommend starting at 45–50 μg/kg/day and possibly increasing up to a dose of 68 μg/kg/day (if the initial response is suboptimal), administered subcutaneously seven days a week, preferably at night.[3] Height should be monitored every 3–4 months in the first year of therapy and every 4–6 months thereafter and GH can be discontinued after linear growth is complete (bone age of approximately 13.5 to 14 years; height velocity <2 cm/year).[3] Potential risks and benefits of GH therapy should be discussed with the family with careful monitoring for adverse events during therapy. Therapy with GH is generally well tolerated in girls with TS, although they appear to be at a slightly increased risk for intracranial hypertension, slipped capital femoral epiphyses, scoliosis and pancreatitis compared with GH therapy for other etiologies of short stature.[21,22] There is conflicting evidence on whether GH therapy worsens

the already inherent risk of glucose intolerance in TS[23,24] but it is recommended to monitor hemoglobin A1c annually regardless of GH therapy.[3] The measurement of insulin-like growth factor I (IGF-I) is recommended annually in the new consensus guideline, and should be considered after GH dose increases. In order to avoid prolonged exposure to elevated IGF-I concentrations, it is recommended to keep the IGF-I less than 2 standard deviations above the mean for age and decrease the dose of GH if IGF-I is more than 3 standard deviations above the mean for age.[3] In girls with TS older than 10 years of age with poor projected adult height on GH therapy alone, the addition of oxandrolone, an anabolic steroid, may be considered at doses of 0.03–0.05 mg/kg/day.[3,25] Potential side effects of oxandrolone therapy include a slight risk of virilizing effects (acne, clitoromegaly), but should not be a concern when using this dose range.[25] Oxandrolone therapy may improve adult height by 2–5 cm when used concomitantly with GH therapy.[26]

Ovarian insufficiency

Spontaneous puberty has been reported in 14% of TS patients with monosomy X and up to a third of patients with mosaicism.[27] While routine oocyte retrieval is not recommended under 12 years of age, young TS women with normal ovarian function should be counseled about fertility preservation options.[3] The majority of the girls with TS however, require induction of puberty and estrogen/progestin replacement therapy to achieve adequate breast development, uterine maturation and peak bone mass. Gonadotropins (especially follicle-stimulating hormone, FSH) should be monitored annually starting at about age 11 years to confirm hypergonadotrophic hypogonadism prior to pubertal induction.[3] Anti-Mullerian hormone (AMH) and inhibin B measurements have also been shown to predict ovarian insufficiency when found to be low, and AMH is perhaps the best indicator of ovarian reserve.[28,29]

Transdermal 17-β estradiol (TDE) is now the preferred treatment starting around age 11–12 years.[3] Compared with oral estrogens, TDE is thought to be more physiological delivery since it will avoid the first-pass effect in the liver with improved bioavailability.[30,31] A recent meta-analysis showed improved whole body bone mineral density, fasting glucose and total cholesterol with TDE therapy compared with oral estrogens.[32] Fractionated patches and initial overnight application have been attempted to achieve lower and more physiologic dosing but needs further study.[33] The lowest doses commercially available are 14–25 μg TDE patches, which deliver this amount on a daily basis after weekly or twice weekly application. Cutting the patches will enable to start at about 3–7 μg/day, which is the recommended starting dose for pubertal induction and is gradually increased in 6-month intervals to adult doses (up to a 100 μg/day) by 2–3 years of therapy.[3] Progestin supplementation (oral micronized progesterone or medroxyprogesterone) should be started once withdrawal bleeding is noted or after about 2 years of estrogen therapy to minimize the risk of endometrial cancer due to unopposed estrogen effect.[3] Despite some reported benefits on cognition, memory, growth velocity, bone health and pubertal onset,[17,34,35] routine supplementation of very low dose estrogen in childhood, to improve growth or bone mass, is currently not recommended.[3]

Neurocognitive/behavioral problems

TS is generally associated with normal intelligence but characteristic challenges and strengths in specific neurocognitive and psychosocial domains. About 10% of girls with TS (particularly those with a small ring X karyotype) may present with intellectual disability.[36] Challenges in executive functioning (task handling, working memory and processing speed), visual–spatial perception, mathematics and reading comprehension, facial expression recognition, motor coordination and motor learning as well as autism spectrum disorders, and, attention deficit and hyperactivity disorder (ADHD) are common in TS.[36–40] Individuals with TS tend to overcome some of these difficulties with superior receptive and expressive language skills.[41] Prompt recognition of neurocognitive challenges and generic psychological remediation techniques with particular accommodations can help improve academic performance and social wellbeing in children with TS.[36,42] For instance, executive function problems can be improved with cognitive behavior therapy and classroom modifications while smaller classrooms, occupational and physical therapy can help with visual–spatial, motor and developmental coordination disorders. Medications for ADHD, and use of verbal mnemonics and oral/untimed testing can also enhance academic achievement.[3,36,42] Because of this it is recommended that children with TS be screened annually for developmental and behavioral issues and undergo formal neuropsychiatric testing at

major transitional stages (preschool, school entry and entry to high school).[43] Having a clinical psychologist or neuropsychologist as a key member of the multidisciplinary team or coordination with a school psychologist can facilitate screening and intervention for these children.[3] Lower self-esteem, social isolation, anxiety and depression may also be common in adolescents with TS[44] and should be recognized and addressed in a timely manner.[42]

Other comorbidities

Cardiovascular abnormalities are common in TS and an important cause of early mortality.[45] Congenital heart defects [e.g. bicuspid aortic valve (BAV), aortic valve stenosis, coarctation of the aorta, aberrant right subclavian artery, hypoplastic left heart syndrome, atrial and ventricular septal defects, partial anomalous pulmonary venous drainage, pulmonary valve stenosis], aortic root dilatation and aortic dissection, ischemic heart disease and cerebrovascular disease contribute to nearly 50% of the excess morbidity in TS.[46] Prenatal detection of TS should prompt a fetal echocardiogram and referral to pediatric cardiology.[3] Surveillance for aortic root dilatation, treatment for hypertension and prophylactic medical therapy with timely surgical consultation is essential to reduce the incidence of aortic dissection (risk is 1 in 40 per 100,000 TS person years), which also appears to occur several decades earlier than in the general female population.[47] The latest consensus guidelines assign girls with TS aged $<$16 years into low, moderate and high-risk categories based on a TS-specific Z-score of the aorta and recommend transthoracic echocardiogram and pediatric cardiology follow up every 5 years, 1–2 years and 6 months to 1 year respectively.[3] In individuals with TS over the age of 16 years, the ascending aortic size index (ASI), defined as the aortic diameter in cm corrected for body surface area, is a useful prognostic indicator and, has been used to categorize risk (2–2.3 cm/m^2 is moderate risk and $>$2.3 cm/m^2 is high risk) and suggest therapy in the latest guidelines.[3] Participation in sports is restricted to low and moderate static and dynamic activities in the moderate risk category while girls in the high-risk category should avoid competitive sports and intense weight training.[3] Assisted reproductive techniques are contraindicated as pregnancy is considered risky in women with TS who have an ascending ASI $>$ 2–2.5 cm/m^2. Such a high-risk pregnancy, if occurring, would have to be managed with strict treatment of pregnancy-associated hypertension. The pregnant patient would need to be closely followed with frequent cardiac imaging and consideration of prophylactic surgery if rapid aortic enlargement is observed.[3,48]

The recommendations to screen for cardiovascular abnormalities and other common comorbidities in TS are summarized in Table 1.[3] A multidisciplinary team approach will help optimize the health care delivery for TS and improve compliance/adherence and clinic attendance. External ear abnormalities, increased risk of (chronic) otitis media and early onset sensorineural hearing loss are common in TS with an age-related increase in incidence of hearing loss.[49] Multiple autoimmune diseases, such as chronic lymphocytic thyroiditis, celiac disease, inflammatory bowel disease (especially Crohn's disease), are also commonly associated with TS, but the pathophysiologic mechanism of immune alteration remains unclear.[50]

Transition to adult care

Transition of young adults with TS to adult care is especially important with due recognition of the core elements of transition, namely: assessment of transition readiness, a transfer summary and a self-assessment tool kit.[3] It is now recommended that pediatric practices use TS-specific transition tool kits (such as the one developed by the Endocrine Society, Hormone Health Network and Turner Syndrome Society of the US, the American College of Physicians Pediatric to Adult Care Transitions toolkit: https://www.acponline.org/system/files/documents/clinical_information/high_value_care/clinician_resources/pediatric_adult_care_transitions/endo_turner/endo_ts_transition_tools.pdf). TS advocacy and peer support groups have additional resources that may be made available to girls with TS and their families. Care for adults with TS is ideally delivered in a multidisciplinary setting with gynecology, cardiology, endocrinology and gastroenterology among other specialties. Obesity, insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, sensorineural hearing loss, hypertension, and hyperlipidemia are common comorbidities in adult women with TS and require repeat screening and appropriate management.[51] Surveillance for aortic root dilatation and treatment of other cardiac abnormalities by a cardiologist familiar with the care of adults with congenital heart diseases is very important. Dual energy X-ray absorptiometry (DXA) scans every 5 years and continued estrogen

Table 1. Recommended screening for comorbidities in childhood in Turner syndrome.

Comorbidities	Common abnormalities	Screening recommendations
Cardiovascular	BAV CoA Aortic root dilatation Other (left-sided) cardiac anomalies (see text) ECG and cardiac conduction defects Hypertension Hyperlipidemia	1. TTE at diagnosis 2. Resting ECG and QTc (Hodge's formula) measurement at diagnosis 3. Monitoring of aortic root diameter and medical and surgical management 4. CMR as soon as feasible without need for general anesthesia 5. In the absence of BAV or CoA, TTE or CMR surveillance every 5 years; annually if BAV or CoA present or the TS-specific aortic size Z-score>3 6. If >16 years, and ASI > 2–2.3 cm/m^2, annual TTE or CMR recommended 7. Annual assessment of blood pressure and prompt medical treatment of hypertension 8. Annual lipid profile starting at age 18 years
Otorhinolaryngological	Early onset sensorineural hearing loss Middle ear infections External ear abnormalities	1. Audiometric evaluation every 5 years starting at 9–12 months of age 2. Treatment of middle ear infections and myringotomy tube placements as needed
Ophthalmologic	Refractive errors Amblyopia Strabismus Ptosis	Comprehensive ophthalmologic examination at 12–18 months or at diagnosis in older girls with TS and annually thereafter
Dental	Abnormal tooth eruption and root and crown abnormalities	Dental and orthodontic evaluation at diagnosis and annually
Thyroid	Autoimmune thyroiditis and hypothyroidism	Screen for hypothyroidism at diagnosis and annually thereafter with thyroid studies
Metabolic	Obesity Glucose intolerance	1. Annual screening for hemoglobin A1c and fasting plasma glucose starting at age 10 years 2. Counseling on nutrition and physical activity to maintain healthy weight
Gastrointestinal	Celiac disease Transaminitis IBD	1. Screen for celiac disease at 2-3 years of age and every 2 years thereafter 2. Monitor liver function tests annually starting at age 10 years 3. Symptoms of abdominal pain, weight loss, diarrhea or GI bleeding should prompt evaluation for IBD
Kidneys	Horseshoe kidney Hypoplasia Renal ectopia	Renal ultrasound recommended at diagnosis
Orthopedic	Scoliosis, kyphosis, vertebral wedging, flat feet, cubitus valgus, genu valgum, pectus excavatum, patellar laxity and other musculoskeletal problems	1. Annual examination for scoliosis or every 6 months (if on GH therapy) 2. Assess for abnormalities at 5–6 years and at 12–14 years
Bone health	Vitamin D deficiency Osteoporosis Increased fracture risk	1. Screen for vitamin D deficiency with a 25-OH vitamin D concentration between 9–11 years and every 2–3 years thereafter 2. DXA scans to monitor bone health after adult hormone replacement has been initiated and every 5 years thereafter, and at discontinuation of estrogen therapy at menopause
Dermatologic	Melanocytic nevi	Surveillance if change in nevi size/appearance

ASI, aortic size index; BAV, bicuspid aortic valve; CMR, cardiac magnetic resonance imaging; CoA, coarctation of aorta; DXA, dual energy X-ray absorptiometry; ECG, electrocardiogram; GH, growth hormone; GI, gastrointestinal; IBD, inflammatory bowel disease; QTc, corrected QT interval; TS, Turner syndrome; TTE, transthoracic echocardiogram.

supplementation until ordinary menopausal age can help optimize bone health and prevent osteoporosis in women with TS.[3] Psychosocial issues, career and interpersonal relationships, sexual function, contraception and fertility options should also be discussed with adequate counseling support in adult TS clinics.[51]

Conclusion

The newest management guidelines for TS are still based on expert consensus and the evidence for optimal hormone replacement throughout the age spectrum in TS is still evolving. However, with adequate support and medical care, individuals with TS can reach their full potential with improved health-related and overall quality of life. A multidisciplinary team approach, early recognition and management of the cardiovascular abnormalities, psychoeducational challenges and comorbidities associated with TS, timely introduction of hormonal therapy, as well as a good transition care plan to adulthood are important to achieve the best quality of life outcomes for these individuals.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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