Review Article

Turner syndrome: narrative review of genetics and clinical aspects of management

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Background and Objective: Turner syndrome (TS) is a genetic condition that is associated with a wide array of clinical manifestations including short stature, ovarian failure, autoimmune diseases, cardiovascular disease, osteoporosis, metabolic syndrome and type II diabetes, as well as neurocognitive deficits in some individuals. TS is associated with loss of all or part of the second sex chromosome, and occurs in approximately one in 2,500 live-born females. The diagnosis is often made at birth in those individuals with more specific manifestations of the disorder, however many girls and women are diagnosed later in childhood or adolescence due to mild clinical features. Individuals with TS have increased morbidity and mortality compared to the general population necessitating increased awareness and improvements in clinical care. This narrative review will present an overview of the genetic mechanisms of TS and aspects of clinical management with a focus on four areas: short stature, gonadal failure, cardiovascular disease and neurocognitive deficits.

Methods: A literature search of PubMed and Cochrane databases was conducted related to each topic included in this article from September 1, 2021 until the time of submission. Articles were selected by the author with focus on peer-reviewed articles, guidelines, and systematic reviews, and were limited to those in English language. Case reports were excluded. Eighty-four articles were selected for inclusion in this review.

Key Content and Findings: In this narrative review, the genetic mechanisms of TS are explored, as well as recent advances in clinical management of four areas including short stature, gonadal failure, cardiovascular disease and neurocognitive deficits. Current clinical care guidelines are discussed, as well as need for further research in some of these areas. TS is a complex disorder necessitating multidisciplinary care.

Conclusions: Improvements have been made in our understanding of some aspects of TS, while others have yet to be elucidated and require further research. This review provides an update on the most common aspects of clinical care and recently described genetic mechanisms. Clinical care guidelines for TS are available which recommend life-long surveillance for TS associated problems with screening tests at specific ages, as well as management recommendations for comorbidities.

Keywords: Turner syndrome (TS); ovarian failure; short stature; cardiovascular; executive function

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Introduction

Turner syndrome (TS) is a genetic condition which occurs in approximately one in 2,500 live born females, and is associated with characteristic features of short stature, gonadal failure, cardiac anomalies, autoimmune disorders, osteoporosis, and insulin resistance and risk of type 2 diabetes (1). TS occurs in phenotypic females who have one structurally normal X chromosome, and complete or partial absence of the second sex chromosome. TS was first described in 1938 by Dr. Henry Turner, an endocrinologist, who described a syndrome of pubertal delay, webbing of the neck, and cubitus valgus (2). Since its initial description, there has been a vast expansion of knowledge of TS

Table 1 Search strategy for narrative review

Items	Specification
Date of search	September 1, 2021 to August 5, 2022
Databases and other sources searched	PubMed, Cochrane
Search terms	"Turner Syndrome", "genetic", "X chromosome", "mosaicism", "karyotype", "prenatal", "ovarian failure", "estradiol", "hormone replacement", "growth", "stature", "growth hormone", "oxandrolone", "metabolic syndrome", "autoimmune disease", "cardiovascular", "congenital heart defect", "hypertension", "neurocognitive profile", "executive function", "hearing loss"
Timeframe	Publications from inception until search date were considered
Inclusion and exclusion criteria	Peer-reviewed articles, guidelines, systematic reviews were included. Articles limited to English language. Case reports were excluded
Selection process	Articles were selected by one author (E.B.F.) who reviewed and analysed the articles

including recognition of a wide variety of clinical features and genetic contributions to the development of these manifestations. Clinical care guidelines developed by experts in the field provide screening recommendations throughout the lifetime, and guidelines for management of associated disorders (3). These tools provide a framework for clinical management, although controversies exist in some aspects of care. Multidisciplinary clinics may improve quality of care and reduce mortality by promoting communication and improving accessibility among the medical specialties involved. This review aims to provide readers with a comprehensive overview of the current literature on the genetic basis of TS, as well as four aspects of clinical care including short stature, ovarian failure, cardiovascular disease and neurocognition. The author discuss current standards of care, as well as areas in which more investigation is needed. The author present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-22-9/rc).

Methods

A literature search of PubMed and Cochrane databases was conducted related to each topic included in this article from September 1, 2021 until the time of submission, and is summarized in *Table 1*. MeSH words used included Turner Syndrome, genetic, X chromosome, mosaicism, karyotype, prenatal, ovarian failure, estradiol, hormone replacement, growth, stature, growth hormone, oxandrolone, metabolic syndrome, autoimmune disease, cardiovascular, congenital heart defect, hypertension, neurocognitive profile, executive function, hearing loss. Articles were selected by the author with focus on peer-reviewed articles, guidelines, and systematic reviews, and were limited to those in English language. Case reports were excluded. Eighty-four articles were selected for inclusion in this review.

Diagnosis and genetics

Turner Syndrome is diagnosed in females who have lost an entire sex chromosome or part of the X chromosome that includes the tip of the short arm, and who have one or more typical clinical features of the disorder. A standard 30-cell karyotype is recommended for diagnosis of TS, and will identify at least 10% mosaicism with 95% confidence (4). If the standard karyotype is normal and there is high suspicion of TS, more metaphase cells may be counted in the karyotype and additional tissues such as skin fibroblasts or buccal mucosal cells may be genotyped.

TS can be detected prenatally by invasive testing such as amniocentesis or chorionic villus sampling, although false positives may occur and a postnatal karyotype is required for confirmation. Recently, non-invasive prenatal testing has been evaluated for detection of sex chromosome aneuploidies such as TS. These techniques using sequencing or single-nucleotide polymorphism array analysis of cell-free fetal DNA in maternal blood were shown to have a relatively low detection rate (90%) and positive predictive value (23%) in a recent meta-analysis (5). Invasive testing continues to be the recommended method for investigation of fetal karyotype. The presence of ultrasound findings such as increased nuchal translucency, heart defects including coarctation of the aorta or left sided heart defects, renal anomalies, oligohydramnios or polyhydramnios increase specificity of prenatal testing; the presence of cystic hygroma noted on prenatal ultrasound predicts TS in 30–

70% of cases (6,7). Prenatal genetic counseling is important to provide families with the most accurate information about prognosis and potential complications, as well as typical features and quality of life in TS.

Individuals with TS may present with a variety of different karyotypes, and great degree of heterogeneity exists between individuals with TS even with the same karyotype. About half of patients presenting with TS have monosomic 45,X karyotype, 15–30% have mosaicism (at least one other cell line in addition to 45,X), and the remainder have structural X chromosome abnormalities such as isochromosomes, ring X chromosomes or deletions of the X chromosome. Y chromosome material may be present in 10–12% (8,9).

The karyotype does not consistently predict phenotype, however, research suggests that several generalizations can be made about certain karyotype subgroups. In general, individuals with 45,X karyotype tend to have more severe clinical expression of disease, and those with 45,X/46,XX karyotypes tend to have milder phenotypes including physical features, cardiovascular abnormalities and lymphatic disease (10). In addition, those with 45,X/46,XX and other forms of mosaicism have greater chance of preserved ovarian function and higher likelihood of spontaneous pregnancies; however, women with mosaicism are at higher risk of miscarriages and premature menopause compared to the general population (11,12). The presence of Y chromosome material is associated with increased risk of gonadoblastoma (estimated to be about 10% although there is considerable variability between studies), and gonadectomy is recommended in those individuals (13,14). Molecular screening for cryptic Y-chromosome sequences is recommended in those with virilizing features who are negative for Y-chromosome material on conventional karyotype and FISH analyses (15). A ring X chromosome may be associated with varying degrees of intellectual disability in some cases (16,17). Clinical surveillance for associated co-morbidities is recommended in all patients regardless of karyotype (3).

Knowledge about the genetic basis of TS is evolving, and several contributing mechanisms have been elucidated. In normal female somatic cells, one of the X chromosomes is inactivated early in fetal development, however about 20% of the genes on the inactivated X chromosome escape X-inactivation and continue to be expressed. Many of these genes have homologous genes on the Y chromosome (18). The escape genes are candidates for explaining the development of the TS phenotype. The most notable of these is short-stature homeobox-containing gene on the X chromosome (*SHOX*). *SHOX* is a transcriptional regulator expressed in chondrocytes in the growth plate, and thought to be responsible for the skeletal dysplasia of TS including short stature with mesomelia, scoliosis, Madelung deformity, and cubitus valgus, as well as high arched palate and micrognathia (19).

Tissue inhibitor matrix metalloproteinase 1 (*TIMP1*) and *TIMP3* have been linked to increased risk of bicuspid aortic valve and aortic dilation, although additional validation studies are needed (20). Epigenetic mechanisms such as differential methylation and copy number variations may be involved in the development of the TS phenotype. Genome-wide copy number variations were found to be increased in TS in one study which postulated this mechanism as a potential contributor to the development of congenital heart disease in TS (21). Women with TS compared to 46,XX women have a hypomethylated genome with fewer areas of hypermethylation, and differences in RNA expression involving X chromosome and autosomal genes (22). Knowledge about the complex genetic factors involved in the development of the TS phenotype is advancing, which could improve our understanding of this condition, and potentially lead to new therapeutic strategies.

Clinical features

TS is a highly variable disorder with a wide spectrum of clinical characteristics (*Table 2*). Some of the most common features include short stature, ovarian failure, cardiovascular disease and a characteristic phenotype. Classic facial features include flat nasal bridge, hypertelorism, ptosis, epicanthal folds, low-set and prominent ears, and retrognathia. Other common physical stigmata that may serve as diagnostic clues are a broad chest with widely spaced nipples, webbing of the neck, low posterior hair line, scoliosis, Madelung deformity, genu varum and flat feet, as well as lymphedema of the hands and feet.

Diagnosis in infancy is often made due to physical findings such as lymphedema and webbed neck, or due to congenital heart disease; the majority of these infants have 45,X karyotype. TS may be detected in childhood most often due to short stature or poor linear growth, or in the teenage years due to pubertal delay (23,24). In some cases, the diagnosis is delayed until adulthood in those with subtle features who may present with primary or secondary amenorrhea or infertility. In 2005, Massa *et al.* showed a trend for earlier diagnosis using a survey of the Belgian

Table 2 Clinical features of Turner syndrome

Cardiovascular
Bicuspid aortic valve
Coarctation of the aorta
Hypertension
Aortic dilation/aneurysm
Prolonged QT
Dental
High arched, narrow palate
Hypoplasia of mandible/retrognathia
Abnormal dental development
Premature eruption and crowding of teeth
Dermatologic
Multiple nevi
Pilomatrixomas
Psoriasis
Vitiligo
Alopecia
Lymphedema of hands and feet
Endocrine/metabolic
Short stature
Ovarian failure
Autoimmune thyroid disease
Glucose intolerance
Type 1 diabetes
Type 2 diabetes
ENT
Sensorineural hearing loss
Frequent otitis media
Abnormalities of upper airway/obstructive sleep apnea
Gastrointestinal
Transaminitis
Celiac disease
Inflammatory bowel disease
Gastrointestinal vascular abnormalities
Ophthalmologic
Amblyopia
Ptosis
Strabismus
Renal
Horseshoe kidney
Renal aplasia or ectopia
Malformation of collecting system such as duplication of ureters, or abnormalities of renal pelvis or renal vessels
Skeletal
Scoliosis
Decreased bone mineral density
Madelung deformity, cubitus valgus, short fourth metacarpal
Neurocognitive
Nonverbal learning disorder
Attention deficit disorder
Deficits in social cognition
Psychological disorders

Data from Ref (3,7). ENT, ear, nose, and throat.

database, with 30% of girls diagnosed during infancy, 48% between ages 1 and 12 years, and 22% after 12 years of age. The median age of diagnosis was 6.6 years compared to 11.2 years in their previous study in 1991, likely due to increased awareness of TS (24).

After diagnosis, patients and families should be treated in a multidisciplinary center experienced in TS care. Healthcare guidelines and checklists are available to guide health care providers as well as families to ensure all aspects of care are addressed (3). Families should be encouraged to become involved in support groups such as the Turner Syndrome Society, Turner Syndrome Foundation, and Turner Syndrome Global Alliance. In addition, attendance of TS camps and retreats can provide opportunities for interacting with others affected.

Growth failure

Growth failure is the most common feature of TS occurring

in almost all patients. Growth failure sometimes begins prenatally, and often continues into infancy and childhood; most girls with TS demonstrate growth failure within the first 3 years of life (9). There is a progressive decline in linear growth rate during childhood which is compounded by blunted or absent pubertal growth spurt resulting in average adult stature 20 cm less than peers.

Growth hormone (GH) is considered standard of care for girls with TS, and numerous studies have demonstrated acceleration of linear growth, and improvements in height standard deviation score (SDS) and adult stature with GH treatment (3). In a randomized, controlled study of GH treatment in girls to adult height, subjects gained an average of 7.2 cm over a mean of 5.7 years of GH therapy (25). These data are consistent with a 2007 Cochrane Center Review showing average height gains of 5–8 cm over 5.5 to 7.6 years of GH treatment, compared to controls, projected height at baseline or historical controls (26). Overall, the data show that GH therapy appears to result in height gain of about 1 cm per year of treatment, with tendency for greater height gains in the first 2 years of treatment. In patients having robust catch-up growth to the normal range within the first 2 years of treatment, a normal growth velocity is often maintained and an adult height in the low normal range can be reached (around 60 inches or greater) (3).

Factors which predict taller adult height and treatment response are younger age and taller stature at initiation of therapy, longer length of treatment, longer length of treatment prior to pubertal induction, taller parental stature, and higher GH dose (27-30). Although not all of these factors are modifiable, they can be informative for patients and families about expectations from GH therapy. Preliminary studies evaluating genetic markers predictive of response to GH have identified potential genomic mechanisms (such as common genes and differential methylation) which could contribute to the variability in response to GH (31,32). Further investigation is necessary to validate pharmacogenetic models which could aid in individualizing clinical management.

Given the expected decline in linear growth in early childhood, and that duration of treatment is a predictor of taller adult stature, the safety and efficacy of early initiation of GH therapy has been investigated. The Toddler Turner Study was a randomized, controlled trial of GH therapy initiated between ages 9 months and 4 years; this trial showed an increase in height SDS of 1.1 in the treatment group, compared to the control group who declined by 0.5 SDS, resulting in a 1.6 SDS difference in the two groups at the end of the 2-year trial. Importantly, GH was well tolerated with no increase in side effects in this group (33). The French Collaborative Young Turner Study Group showed that initiation of GH treatment in young girls less than 4 years of age (2.6 years on average) resulted in 80% of the treatment group attaining height in the normal range over a 4-year period. GH therapy was well tolerated in this group, although one case of transient glucose intolerance was identified which resolved with dietary modifications (34).

The ideal age for initiation of GH therapy in girls with TS has not been clearly defined, although data suggests younger age at treatment initiation and length of therapy are associated with greater height gains. GH therapy also appears to be safe and effective in younger girls as noted previously. The 2017 TS Clinical Practice Guideline suggests relatively early initiation of GH treatment around ages 4–6 years in girls who have demonstrated growth failure (3). Benefits of earlier treatment include potential for greater height gains, normalization or near-normalization of height and elimination of physical limitations due to stature, and increased likelihood of age-appropriate pubertal induction. GH therapy can be continued until the patient is satisfied with her height, or linear growth is complete (bone age ≥14 years or linear growth rate <2 cm/year).

GH therapy has been shown in general to be safe and well tolerated in TS girls. GH therapy does not appear to have adverse effects on the cardiovascular system including aortic diameters, cardiac function or blood pressure (35,36). In addition, long term studies of GH safety have not found negative effects on bone mineral density, body composition, lipid and carbohydrate metabolism, prevalence of otitis media or hearing loss (37-41). The incidences of increased intracranial hypertension (0.23%) and slipped capital femoral epiphysis (0.24%) appear to be higher in TS girls compared to non-TS patients based on a study including 5,220 girls with TS. Data from this study also showed higher incidences of scoliosis (0.39%), diabetes (0.19%) and cardiovascular events (0.32%), all of which are associated with TS without GH therapy (42). Treatment with GH may have favorable effects on body composition and fat distribution leading to improvement in insulin sensitivity and glucose tolerance, as well as beneficial effects on lipid profiles and blood pressure (43). Health related quality of life (HRQOL) has been shown to be normal in adults with TS who received growth hormone and estrogen therapy, however more recent data from long-term randomized controlled trials have shown no benefit or adverse effect of

GH therapy on HRQOL (44,45).

Typical doses of GH used in TS are 0.315–0.35 mg/kg/week divided seven days per week. Clinical monitoring of linear growth during treatment is recommended every 4–6 months, with measurement of IGF-1 levels annually or with dose adjustments. Reduction of GH dose is recommended if IGF-1 value is +3 SDS, and clinical judgment about dose adjustment is suggested in IGF-1 value is between +2 SDS and +3 SDS (3). If growth rate is suboptimal, noncompliance or the development of other problems such as celiac disease or hypothyroidism should be considered.

Oxandrolone, a non-aromatizable androgen, can be considered as an adjunct in girls who are 10 years or older with extreme short stature, or with poor response to GH despite compliance. Oxandrolone has a modestly synergistic effect when given with GH, increasing adult height by 2.3–4.6 cm on average (46,47). Use of oxandrolone can be associated with delayed breast development and virilization (such as deepening of the voice and clitoromegaly) at higher doses; these side effects are minimized at the recommended dosing range of 0.03–0.05 mg/kg/day (47,48).

Ovarian failure

TS is associated with gonadal dysgenesis resulting in gonadal failure in the majority of patients. During the first trimester of fetal life, ovarian development appears to be normal, however accelerated loss of oocytes begins around mid-gestation resulting in progressive fibrosis of the gonads. Oocytes may be depleted by birth, although some girls may continue to have oocytes and functional follicles after birth (49). Girls with TS have an exaggerated biphasic age-related pattern of gonadotropin secretion with high levels during infancy and early childhood, during the time of mini-puberty, which decline during mid-childhood to normal or slightly elevated levels, followed by another rise during adolescence (50). Anti-Mullerian hormone (AMH) is a sensitive and specific marker of follicular reserve and is predictive of the reproductive lifespan; AMH levels <–2 SDS have been shown to be predictive of failure to enter puberty in girls with TS, and imminent ovarian failure in adolescents and adults (51). Low Inhibin B levels may also be predictive of absence of spontaneous puberty, but is a less specific marker (52).

Spontaneous breast development occurs in approximately one-third of girls with TS, but only about 5% have adequate ovarian reserve to progress to menarche (53,54). The likelihood of spontaneous pubertal development and menarche is higher in those with mosaic karyotypes, although almost all patients eventually develop ovarian failure (55). Spontaneous pregnancies are rare in women with TS (2–5%), and are more likely in those with mosaicism (56,57).

Hormone replacement therapy is necessary in most girls and women with TS for induction of pubertal development, and subsequently for maintenance of estrogen dependent processes during adulthood. In girls, the goals of therapy include normalizing the development of secondary sexual characteristics such as breast size and shape, and uterine growth for potential reproductive function, attaining peak bone mass, and positive effects on cardiovascular and liver function. The optimal hormone replacement regimen to achieve these goals is still being investigated, although literature supports the theoretical benefits and effectiveness of transdermal estrogen delivery. Theoretical advantages of transdermal estradiol include avoidance of first pass metabolism resulting in the production of estrogen metabolites which are associated with increase in thrombotic risk and stroke (58,59). In addition, transdermal estradiol allows a more physiologic route and dosing as patches may be cut to administer very low doses which can mimic estradiol levels in early puberty (60).

Recent clinical guidelines recommend beginning low-dose transdermal estradiol at a near physiologic age around 11–12 years if gonadotropins are elevated. If FSH and LH are normal, the patient should be monitored for spontaneous puberty, and replacement initiated if ovarian failure develops. Pubertal induction at physiologic age allows for age appropriate physical and social development and may improve quality of life (45). Importantly, age-appropriate pubertal induction does not appear to compromise adult stature and the beneficial effects of GH therapy with concomitant low dose estradiol therapy may modestly increase adult height (30,61).

Several protocols for pubertal induction have been published (3,62). Common features of treatment protocols are the use of low-dose transdermal estradiol beginning at a physiologic age, with incremental dose increases over a 2- to 3-year period to mimic the normal tempo of puberty. Progestin therapy is added when breakthrough bleeding occurs, or after 2 years of estrogen therapy due to risks of endometrial hyperplasia and endometrial cancer with prolonged unopposed estrogen exposure. The progestin may be taken for 10 days per month which will result in menstruation, or be taken as combined continuous therapy

with estrogen which will prevent menses. Both of these regimens of progestin administration have been shown to be protective against endometrial hyperplasia (62), and the regimen can be guided by patient preference. Progestin forms vary based on their ability to exert activity on glucocorticoid, mineralocorticoid and androgen receptors in addition to progesterone receptors; these differential effects may potentially result in unique metabolic changes. Recently, a study by Mathez suggested that levonorgestrel was associated with less weight gain in adult TS women compared to medroxyprogesterone and micronized progesterone (63). Further research is needed to delineate the long-term metabolic effects of various forms of hormone replacement therapy.

In addition, hormone replacement regimens may be individualized based on patient desire about tempo of pubertal development or concerns about stature. A patient who is diagnosed later in childhood or adolescence, or in whom GH therapy has been delayed may wish to optimize growth; in these cases, GH treatment prior to pubertal induction is reasonable and lower dose estrogen doses may be used longer. However, pubertal induction should not be delayed beyond 14 years of age due to potential negative effects on bone health and psychosocial functioning (62).

After completion of puberty and linear growth, hormone replacement therapy should be continued at adult replacement doses until the time of normal menopause (51 to 53 years) unless otherwise contraindicated. Benefits of continuing replacement throughout adulthood include maintenance of bone health, and positive effects on cardiovascular function, liver function, cognition, and sexual function (64). Patient education about the benefits and risks of continuation of therapy is important, and should be addressed at transition from pediatric to adult care.

Cardiovascular disease

Girls and women with TS are at increased risk of cardiovascular disease, both congenital and acquired. A three-fold higher mortality rate has been shown in TS compared to the general population, and cardiovascular disease accounts for 41% of this increased mortality (65). Congenital heart disease occurs in approximately 50% of live-born girls with TS with the most common defects being bicuspid aortic valve (16%) and coarctation of the aorta (11%) although other structural anomalies such as atrial and ventricular septal defects, partial anomalous pulmonary venous return, and persistent left superior vena cava can be seen (66). Due to the high frequency of structural defects, all patients should be evaluated with cardiac imaging at diagnosis even if fetal imaging was normal. Transthoracic echocardiography is often sufficient in infants and young girls, and cardiac MRI should be performed when the study can be done without sedation. Electrocardiographic abnormalities such as QTc prolongation have been described in TS and patients should have an electrocardiogram as part of their cardiac assessment. Individuals with TS should be evaluated at diagnosis by a pediatric cardiologist with expertise in TS related heart disease, and receive ongoing monitoring for screening and management of cardiovascular disease (3).

A generalized vasculopathy is thought to affect individuals with TS, predisposing to aortic dilation and increased risk of aortic dissection. Aortic dissection is often fatal and occurs in approximately 1% of individuals with TS at a median age of 35 years (67). Imaging studies have shown aortic dilation (defined by aortic diameter >95th percentile normalized for body surface area) to be present in about one third of women with TS (68). Aortic dilation often precedes dissection necessitating close monitoring of aortic size in TS, and clinical care guidelines outline suggested frequency of imaging based on age and degree of aortic dilatation (3).

Individuals with TS have increased risk of acquired cardiovascular disease such as coronary artery disease, cerebrovascular disease, and hypertension. Hypertension affects up to 50% of girls and women with TS and should be treated aggressively as it is a modifiable risk factor for cardiovascular events (69). Comorbidities such as obesity, hyperlipidemia and insulin resistance/type II diabetes also contribute to the development of cardiovascular disease. Patients should receive ongoing screening for these comorbidities as well as counseling about healthy lifestyle choices including regular cardiovascular exercise, healthy diet and avoidance of smoking. Medical management of hyperlipidemia and type II diabetes is necessary is some individuals.

Neurocognition

Most individuals with TS have intelligence within the average or low-average range, with approximately 10% having intellectual disability. A unique cognitive profile has been recognized with strengths in verbal domains and weaknesses in executive functioning and visual-spatial areas (70). In addition, impairments in social and emotional cognition commonly occur. This pattern of traits which is

similar to nonverbal learning disorder (NLD), occurs to a variable degree in those with TS (71).

Hearing loss, both conductive and sensorineural, is common in TS and may be detected in early childhood. The risk of sensorineural hearing loss increases with age and over half of adult women are affected (72). Hearing deficits may interfere with cognitive functioning, making regular audiological screening and treatment of hearing deficits imperative.

Executive functioning and visual-spatial deficits are the most common cognitive impairments in TS. Executive deficits can manifest as difficulty planning, organizing, and problems with working memory. Processing speed, an executive skill, is frequently decreased, leading to problems with performance on timed tests. Abstract reasoning and mental flexibility are areas of weakness, and can lead to difficulty summarizing concepts and transitioning between tasks (70,73). About 25% of school-aged girls with TS are diagnosed with attention-deficit hyperactivity disorder (ADHD), and the management of ADHD is similar to that in the general population (74). Visual-spatial challenges contribute to poor academic achievement in mathematics and motor impairments affecting coordination and fine motor skills (75). Neuroimaging studies suggest that structural and functional differences in frontal, parietal and temporal regions are linked to deficits in executive and visual-spatial deficits (76-78).

In general, verbal skills tend to be an area of strength, although deficiencies in components of verbal processing which are more dependent on executive and visual-spatial function can be seen. For example, deficits in verbal fluency, and ability to interpret the overall concept or meaning of language have been shown (71,79). Individuals with TS may have enhanced linguistic knowledge and tend to use more complex (low-frequency) words on verbal testing. Phonological processing (ability to break down larger complex words and speech into smaller units) is an area of relative strength, and girls with TS were shown to have the ability to pronounce longer and unfamiliar words when compared to age-matched peers (80).

Due to the risk of specific cognitive deficits, neuropsychological testing is recommended at preschool age, entry to elementary school, transition to high school, or any time that academic difficulties come to attention. Interventions such as school accommodations and academic support should be tailored to individual needs. Parent management training may be beneficial for girls affected by executive deficiencies and ADHD. In addition, referral for developmental interventions such as speech, occupational or physical therapy should be considered based on the observed deficits (3).

Social cognition

Social cognition can be problematic in TS, with self-reported issues of anxiety, depression, low self-esteem and impairments in social competence. TS women have a tendency for attaining employment below the level anticipated for the degree of education, as well as an increased likelihood of living with parents during adulthood (81-83). Impaired social cognition in TS is associated with deficits in facial recognition, and interpreting emotional affect from facial expressions. Eye gaze processing has been shown to be atypical in women with TS, and may contribute to social deficits. In addition, higher cognitive processes such as interpreting emotional states or intentions from social cues may be impaired in women with TS (84). Increasing knowledge about the cognitive profile of TS will allow individuals to receive tailored academic and psychological interventions to maximize their academic success and social functioning.

Conclusions

TS is a common genetic disorder associated with a wide array of clinical stigmata including short stature, ovarian failure, cardiovascular disease, neurocognitive deficits, as well as autoimmune diseases and type 2 diabetes. Our knowledge of the genomic mechanisms of TS has advanced including epigenetic changes which may help our understanding of phenotypic features. Improvements have been made in some aspects of clinical care in TS, while others require further research. GH therapy is considered standard of care for treating growth failure and appears to be safe and well tolerated. Hormone replacement is necessary in most girls and women; the optimal hormone replacement regimen is still being investigated, although literature supports the theoretical benefits and effectiveness of transdermal estrogen delivery. Future research is needed to determine the optimal timing, dosing and route of hormone replacement. Cardiovascular disease contributes to increased mortality in TS, and screening is necessary at diagnosis and regular intervals by a cardiologist with experience in TS. Neurocognitive deficits are common, and neuropsychological testing is recommended as well as interventions tailored to specific areas of weakness. Hearing

loss, both conductive and sensorineural, occurs frequently; regular audiological screening and treatment of hearing deficits is imperative due to impact on quality of life and cognitive functioning. Given the complexities of care in these individuals, a multidisciplinary, consolidated approach is optimal.

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Footnote

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