



Turner syndrome: update on biology and management across the life span

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Purpose of review

We review recent understanding of the pathophysiology, molecular biology, and management of Turner syndrome.

Recent findings

Sophisticated genetic techniques are able to detect mosaicism in one-third of individuals previously thought to have monosomy X. Prenatal detection using maternal blood should permit noninvasive detection of most fetuses with an X chromosome abnormality. Disproportionate growth with short limbs has been documented in this condition, and a target gene of short stature homeobox, connective tissue growth factor (*Ctgf*), has been described. Liver disease is more common in Turner syndrome than previously recognized. Most girls have gonadal failure. Spontaneous puberty and menarche is more commonly seen in girls with XX mosaicism. Low-dose estrogen replacement therapy may be given early to induce a more normal onset and tempo of puberty. Oocyte donation for assisted reproduction carries a substantial risk, particularly if the woman has known cardiac or aortic disease. Neurodevelopmental differences in Turner syndrome are beginning to be correlated with differences in brain anatomy.

Summary

An increased understanding of the molecular basis for aspects of this disorder is now developing. In addition, a renewed focus on health maintenance through the life span should provide better general and targeted healthcare for these girls and women.

Keywords

aortic dissection, estrogen therapy, recombinant growth hormone therapy, short stature, Turner syndrome

INTRODUCTION

Since the clinical observations of Turner in 1938, identification of the causative X chromosome monosomy in 1959, and more complete delineation of the distinctive features of Turner syndrome in 1963, the 'phenotype' for both complete and mosaic forms of Turner syndrome has been greatly expanded [1–4] and management through the life span has been more fully addressed [5,6]. In this review, we update the complex biology of this condition, and discuss newest aspects of treatment, long-term outcomes, and the development of multi-specialty clinics devoted to Turner syndrome [7,8]. We also recommend a collection of short autobiographical essays edited by the mother of a young woman followed by the co-authors [9^{***}]. In this unique book, women with Turner syndrome articulate aspects of their lives with passion and wit, and relate incidents that will educate and often humble medical caregivers.

CHROMOSOMAL AND GENOTYPE/ PHENOTYPE CORRELATIONS

Turner syndrome is the result of the absence or structural abnormality of one copy of the X chromosome. Many of the phenotypes result from the absence of the short arm of the X (Xp). A long-arm (Xq) deletion is mostly associated with

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KEY POINTS

- Turner syndrome may be commonly associated with metabolic syndrome, low-grade inflammation, hepatic dysfunction, arterial vessel wall stiffness, and hypertension.
- Approximately, one-third of girls with Turner syndrome, more commonly those with a mosaic XX cell line, will have some spontaneous puberty. Loss of the long arm of the X chromosome leads to infertility and pubertal disturbances but not most of the other findings of the Turner syndrome spectrum.
- The prevalence of aortic dilatation and cardiac disease in Turner syndrome is high and the risk of aortic dissection increases with age. This must be carefully followed.
- Women with Turner syndrome are particularly concerned about infertility. In the USA, Turner syndrome itself is considered a relative contraindication for the use in OD-ART. Studies are needed to determine the natural history and safety of this procedure in a group of women who are eager to become pregnant.
- The development of Turner syndrome research centers in the near future should promote clinical care, education, research, and therapeutic advances.

abnormal menses and infertility [10¹]. Half of the individuals with Turner syndrome have a monosomy X karyotype, whereas mosaicism is identified in the other half. Although mosaicism may be associated with a less-severe phenotype, the degree of mosaicism correlates poorly with phenotype, likely because of heterogeneity in tissue mosaicism [11,12].

The birth prevalence of Turner syndrome has been calculated as 1/2000 live-born girls [13]. A peripheral blood karyotype detects most abnormalities, but a recent study of 187 patients found that a single nucleotide polymorphism (SNP) array was able to detect 100% and provided additional resolution by detecting 13 large copy number variations (CNVs) and two derivative Y chromosomes that were missed by karyotype [14¹]. Microarray was unable to detect the rare presence of three cell lines or balanced translocations involving the X chromosome, but more accurately assessed peripheral blood mosaicism because cell culture may alter ratios of different cell lines.

Hook and Warburton [15¹] recently revisited their hypothesis that all viable girls with Turner syndrome are 'cryptic mosaics'. The loss of the X chromosome in 45,X embryos arises mainly by mitotic error. Therefore, the X chromosome could be lost at various points postfertilization. Efforts to detect cryptic mosaicism in 45,X patients have been

moderately successful. By counting more cells during karyotype analysis, examining additional tissues, or using SNP microarrays, fluorescent in situ hybridization, and PCR, mosaicism was identified in 30% of apparently nonmosaic 45,X patients [16,17]. Hook and Warburton [15¹] hypothesized that two copies of Xp are necessary during embryonic development and propose the placenta as the required location of a 'rescue cell line' in monosomy X. Placentas with Turner syndrome have not been examined for such cryptic mosaicism.

Absence or structural abnormality of the second X chromosome is associated with marked phenotypic diversity. This could result from mosaicism, incomplete X inactivation, X chromosome imprinting, and gene-dosage effects. Only haploinsufficiency of the short stature homeobox (*SHOX*) gene has been linked to a specific phenotype of short stature and skeletal deformities [18,19]. If imprinted genes exist on the X chromosome, the parental origin of the X chromosome could impact phenotypic diversity. Some neurologic and cardiovascular variability has been attributed to parental origin of the X chromosome, which is the maternal X (X^m) in 80% of cases [20], although no specific genes have been strongly implicated [21].

A number of ancestral genes have been retained on the X and Y chromosomes [22¹]. Haploinsufficiency of these genes could cause some of the Turner phenotype because most escape X inactivation, are upregulated in the zygote, and are widely expressed in adult tissues. Most do not appear to be haplolethal.

Recently, transcriptional analysis in Turner syndrome has identified changes in gene expression on all chromosomes. RNA microarrays on five cell-free amniotic fluid samples from 45,X fetuses compared with five 46,XX fetuses identified 470 differentially expressed genes with enrichment for genes involved in the hematologic/immune and neurologic systems [23]. Differentially expressed genes have also been identified in a 45,X fibroblast cell line [24] and an induced pluripotent monosomy X stem cell line [25]. Larger sample sizes will be needed to learn more about the genes that contribute to the Turner phenotype.

PRENATAL DIAGNOSIS

Use of cell-free fetal DNA (cffDNA) or noninvasive prenatal testing has permitted diagnosis of some fetuses with Turner syndrome early in gestation. Sex chromosomes are hard to evaluate in cell-free fetal DNA because of mapping challenges from the small size of the Y chromosome and similarity between the Y and the X autosomal regions. Maternal or fetal mosaicism for sex chromosome

abnormalities will complicate the analysis – about 0.25% of phenotypically normal women have a sex chromosome abnormality [26]. Studies in high-risk pregnancies to identify 45,X reported sensitivities of 93.8–100% and specificities of 99.7–99.8% [26–29]. A false-positive rate of 0.2–0.3% is low, but might still lead to increased invasive testing. Noninvasive prenatal testing currently detects nonmosaic monosomy X, but may miss a structurally abnormal X chromosome or mosaicism.

GROWTH

Girls with Turner syndrome have skeletal disproportion including micrognathia, high-arched palate, short fourth metacarpals, genu valgum, Madelung wrist deformities, and short limbs [30]. Early treatment with pharmacologic doses of recombinant human growth hormone effectively increases adult height, but there are still important concerns related to diagnosis, pathophysiology, and treatment.

Growth charts and their interpretation

Early diagnosis of Turner syndrome based on short stature could improve outcomes. However, identification of short stature may depend upon region-specific growth standards. For instance, use of internationally accepted WHO growth curves might lead to delayed diagnosis of 50% of Finnish girls with short stature [31]. Turner-specific growth curves have been constructed but these too are population based and may not be easily generalizable [32].

Disproportionate growth

In a recent study, the mean sitting height/height Standard Deviations (SDS) for normal girls was 0.1 ± 0.9 , whereas for girls with Turner syndrome, it was 1.9 ± 1.6 [30]. This is related to the absence of one *SHOX* gene on the missing X chromosome but other short stature genes may be involved. *SHOX* regulates growth plate assembly and extracellular matrix during long bone development by transcriptionally regulating connective tissue growth factor gene (*Ctgf*), which controls chondrogenic and angiogenic differentiation [33*].

Treatment of short stature

Growth hormone-induced growth in girls with Turner syndrome and individuals with an isolated *SHOX* gene mutation seems similar. The average adjusted height SDS gain over an average of 7.4 years of daily growth hormone treatment in girls with Turner syndrome was 1.32 ± 0.22 and the average

adult height reached was greater than $-2SD$ in 32% of the girls with Turner syndrome [34]. New studies continue to show excellent growth velocity in the first years of fixed-dose growth hormone treatment, with gradual slowing of response thereafter [35]. Parental origin of the X chromosome does not influence the response [36], but polymorphism in son of sevenless homolog 2, an intracellular negative regulator of growth hormone receptor signaling, [37] and growth response genes ranging from *lim homeobox 4* to intracellular signal transduction genes such as *PTPN1* and the *MAPK* pathway influence growth hormone-induced growth in girls with Turner syndrome [38]. Growth prediction models based on large databases of children with Turner syndrome can help determine the most effective growth hormone dosing and may achieve some economy of growth hormone usage [39]. No new adverse effects of growth hormone therapy have been specifically reported in Turner syndrome in recent years, although there is ongoing controversy about long-term adverse effects [40].

The nonaromatizable androgen, oxandrolone, enhances growth in growth hormone-treated girls with Turner syndrome. Addition of oxandrolone to growth hormone therapy increased adult height by 2.3–4.6 cm in three recently reviewed studies [41]. Side-effects included voice deepening and clitoromegaly. The authors suggest that oxandrolone should be considered as an adjunct in girls who are particularly short and would likely remain so if treated with growth hormone alone.

Finally, a review of limb lengthening surgery in 18 clinical studies of 547 patients included 77 with Turner syndrome, who were noted to have more adverse sequelae and poorer healing than individuals with hypochondroplasia, achondroplasia, or constitutional short stature. This was thought to be due to other medical problems associated with Turner syndrome [42]. This surgery is not commonly recommended to enhance adult height in Turner syndrome in the USA.

BODY WEIGHT AND METABOLIC ISSUES

Turner syndrome increases lifetime risk for type 2 diabetes mellitus and degenerative cardiovascular disease. It is also associated with hepatic and muscle dysfunction.

Metabolic syndrome and diabetes

Metabolic risk markers were examined in girls with Turner syndrome compared with controls [43]. Blood pressure, heart rate, lipids, C-reactive protein, waist circumference, and subcutaneous adipose

tissue mass were higher in girls with Turner syndrome without known cardiac disease. None of the controls and 26% of the girls with Turner syndrome had impaired fasting glucose or glucose intolerance. Growth hormone therapy increases insulin resistance and could have other effects on metabolism in Turner syndrome. A recent study revealed improvement in lipid and protein metabolism during growth hormone treatment, but glucose abnormalities and insulin resistance remained stable [44]. The macrophage marker sCD163, linked to states of low-grade inflammation such as obesity and diabetes, is increased in women with Turner syndrome and decreases following estrogen treatment [45]. Estrogen might reduce the inflammatory state of relatively inactive and overweight women with Turner syndrome.

Hepatic dysfunction

The most common liver abnormality in Turner syndrome is hepatic steatosis or nonalcoholic fatty liver, which is associated with obesity, insulin resistance, and metabolic syndrome. It does not seem to be worsened by estrogen therapy. Other liver abnormalities including autoimmune liver disease, cirrhosis, and biliary lesions are reported [46,47^{*}]. Liver disease is rarely severe, but screening should be conducted yearly.

Muscle function and metabolism

Girls and women with Turner syndrome have decreased muscle power, greater aerobic stress during exercise, and may have more muscle fatigue [48,49]. Muscle mitochondrial metabolism and oxygen transport are normal.

AUTOIMMUNITY

Perhaps because of haploinsufficiency of X chromosome immunomodulatory genes, women with Turner syndrome are at increased risk of autoimmune disorders. Antithyroid antibodies are common, whereas celiac, diabetes, and adrenal antibodies are rare. Many patients with positive antibodies do not have associated disease [50,51]. However, a British record-linked data set of 2459 women with Turner syndrome demonstrated that hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, celiac disease, and inflammatory bowel disease were significantly more common than in the general population [52^{*}].

GONADAL FAILURE

In 45,X fetuses, the ovaries normally develop until 18 weeks of gestation after which there is accelerated

germ cell loss, resulting in a severe impairment of folliculogenesis and an increase in connective tissue ultimately giving rise to the characteristic 'streak gonad'. The mechanism for ovarian failure has not been definitively established. Haploinsufficiency of X-linked genes that escape X chromosome inactivation would not explain why some 45,X patients have spontaneous puberty unless one postulates that low levels of mosaicism were being missed by standard karyotyping. An alternative possibility is that copy number variants (CNVs) affecting genes important for female fertility might also contribute to the phenotype. A recent study of 40 patients with Turner syndrome used genetic and molecular cytogenetic analyses to evaluate X chromosome mosaicism and detect possible rare CNVs in genes known to impact ovarian function [12]. Six patients had spontaneous menarche and 34 had primary amenorrhea. Mosaicism for 46,XX was significantly higher in those with spontaneous menarche (67 versus 12%). The authors postulate that 10% mosaicism for the euploid cell line determined by molecular cytogenetic techniques may predict spontaneous puberty. In addition, a few CNVs involving ovary-related loci were identified in both X-linked and autosomal ovary-related genes suggesting that gene dosage may contribute to the ovarian phenotype. About one-third of girls with Turner syndrome, most of whom have mosaicism, undergo spontaneous puberty. There is likely to be selection bias, because in girls diagnosed before the age of 10 years, 16/32 (50%) entered puberty spontaneously compared with 18/63 (28.6%) girls diagnosed after the age of 13 years [53].

Sex steroid replacement

Timing of introduction of sex steroid replacement is critical. It is important not to initiate treatment in girls who will have spontaneous puberty. Follicle-stimulating hormone (FSH) and anti-Mullerian hormone (AMH) levels have been used to identify prepubertal girls with gonadal failure. FSH levels tend to be higher in girls with Turner syndrome in the first few years of life, but there is overlap with normal girls during mid-childhood, limiting its diagnostic utility [54]. AMH is expressed in granulosa cells of growing follicles and a decline in AMH has been shown to precede changes in FSH [55]. In a cross-sectional analysis of 270 girls with Turner syndrome, serum AMH was detectable in 21.9%, most of whom had the 45,X/46,XX karyotype [56^{**}]. Menarche was 47.6 times (odds ratio) more likely with detectable AMH levels. Similarly, spontaneous puberty was reported in 58.3% of girls with measurable serum AMH versus 2.9% of those in

whom it was not detectable. Although limited by its cross-sectional design, this study suggests that AMH may be a sensitive marker of follicle pool in prepubertal girls with Turner syndrome.

Consensus guidelines now recommend initiating low-dose estradiol therapy at the age of 12 years [7]. A low-dose estrogen patch can be applied at night to try to reproduce the nocturnal pattern of estrogen secretion of early puberty [57]. Starting doses may be as low as one-tenth of standard adult replacement and are gradually increased to achieve optimal breast and uterine development. Some have advocated a weight-based regimen with starting doses of 0.05–0.07 $\mu\text{g}/\text{kg}$ to mimic physiological estradiol levels and subsequent increases to 0.08–0.12 $\mu\text{g}/\text{kg}$ to maximize breast growth [57]. Addition of a progestin is deferred for about 2 years unless breakthrough bleeding occurs. Although oral contraceptives should not be used to induce puberty, they can be substituted once puberty is complete. Unless there is a contraindication, estrogen therapy should be continued until the time of normal menopause.

Initiation of ultralow-dose estrogen replacement as early as 5 years of age has been proposed [58[¶]]. In a randomized, double-blind placebo-controlled trial of 149 girls with Turner syndrome, individualized childhood estrogen replacement with ethinyl estradiol followed by an escalating pubertal induction regimen resulted in a more physiological onset of puberty – significantly earlier thelarche (11.6 versus 12.6 years) and a slower tempo of puberty (3.3 versus 2.2 years).

Oral and transdermal estrogen are equally effective in inducing secondary sex characteristics and preserving bone health. However, a recent randomized clinical trial of 40 girls with Turner syndrome suggests that transdermal 17 β -estradiol yields a more physiologic estrogen milieu than its oral counterpart, although no difference in body composition, bone density, or metabolic parameters were identified at 6 months [59]. Although not specifically studied in women with Turner syndrome, postmenopausal women have an increased risk of thromboembolism with oral versus transdermal estrogen [60].

SEXUALITY

Girls and women with Turner syndrome may have low self-esteem and more shyness and social anxiety than controls. In a population-based study of 566 French women with Turner syndrome, low self-esteem was associated with hearing impairment and limited sexual experience, whereas age at first sexual intercourse was related to age at puberty and paternal socioeconomic class [61]. Given the lasting

effect of delayed puberty on subsequent sexual function, these data highlight the importance of inducing puberty at a physiologically appropriate age.

CARDIOVASCULAR ABNORMALITIES

The type and frequency of congenital heart defects (CHDs) in Turner syndrome has been well studied [62]. Bicuspid aortic valve (BAV) and coarctation of the aorta is found in at least 30% and 12%, respectively. A study reporting that at least 5% of girls with coarctation had Turner syndrome suggests that every girl with a coarctation should have a karyotype [63[¶]]. Individuals with an abnormal X chromosome offer insights into the genomic basis of BAV, a common congenital heart defect [64[¶]]. The spectrum of aortic valve anomalies has been delineated using cardiac MRI. Partially fused aortic valve, BAV, and unicuspid aortic valve were significantly associated with mild aortic regurgitation and elevated peak velocities across the aortic valve [65].

The high prevalence of BAV and coarctation in patients with Turner syndrome and an Xp deletion suggested that haploinsufficiency for genes on Xp contributes to abnormal aortic valve and aortic arch development [66]. Patients with mixed gonadal dysgenesis may have male or female phenotypes depending on the percentage of the cell lines. The cardiovascular abnormalities were similar [67]. Despite this strong association, Turner syndrome and BAV may be overlooked [68].

The association of Turner syndrome and aortic dilation is well recognized, and the observation that vessels beyond that aortic arch may be dilated and have pathologic abnormalities supports the notion of a diffuse vasculopathy [69]. A prospective study of children with Turner syndrome and lean and obese controls revealed increased arterial vessel stiffness in girls with Turner syndrome [70]. The known correlation between arterial wall stiffness and hypertension has implications for natural history and therapy in these girls.

Because of the 100-fold risk of aortic dissection and rupture in women with Turner syndrome, attention has been directed at aortic dilation, which can be detected by cardiovascular MRI in almost 30% of these women. Mortensen *et al.* [71[¶]] noted that coarctation, BAV, age, diastolic blood pressure (DBP), body surface area (BSA), and antihypertensive treatment were associated with dissection, confirming previous work [72]. They also created a mathematical model to identify women with rapid growth of aortic diameter.

Electrophysiologic abnormalities [prolongation of the QT (the interval between the Q wave and the T wave in the electrocardiogram) interval] have also

been reported in Turner syndrome [73,74]. Mutations in the major *long QT syndrome* genes in women with Turner syndrome may explain this finding and suggests that this might account for the higher mortality in this population [74].

REPRODUCTION

Spontaneous pregnancy occurs in a small number of women with Turner syndrome who usually have mosaicism and a milder phenotype. Although oocyte donation-assisted reproductive technology (OD-ART) is technically feasible in women with Turner syndrome, concerns have been raised about the safety because of the small, but potentially lethal, risk from aortic dissection [75,76]. The American Society for Reproductive Medicine publishes clinical guidelines to provide cardiovascular care and surveillance imaging for women who undertake pregnancy [77]. As of 2012, Turner syndrome itself is considered a relative contraindication for the use of OD-ART, and an absolute risk if a major cardiac complication is present. Two large studies report on obstetric, neonatal, and obstetric morbidity in this population [78,79]. In many countries in Europe, OD-ART is performed, but natural history studies are needed to determine the safety of this procedure in women who may have a diffuse vasculopathy in addition to aortic disease.

NEUROPSYCHOLOGY

Girls and women with Turner syndrome generally have a normal verbal Intelligence Quotient (IQ) yet often have lower performance IQ, problems with visual spatial skills, processing visual cues, social difficulties, and executive function [80,81]. They do not have diminished empathy or an increase in true autistic traits [82]. Brain imaging studies in humans and mouse models confirm differences in neurodevelopment. Early pubertal girls with Turner syndrome have increased gray matter volume in parts of the brain that would correlate with impaired visual spatial skills [83]. Other studies have noted similar gray matter changes and alterations in the developmental trajectory of the parietal cortex [81,84,85]. Individuals with a maternal X have greater gray matter volume in the superior frontal regions and lesser cortical thickness in the temporal regions compared with girls with a paternal X chromosome [86]. Similar MRI imaging abnormalities have been reported in a mouse model of the paternally derived X karyotype. Raznahan *et al.* [87] postulated an evolutionarily conserved influence of X-linked genes on cortical and subcortical development in mammals.

Changes in neurobehavior and anatomy may not be entirely fixed. Earlier diagnosis and appropriate

treatment might improve autonomy as well as adult psychosocial functioning [88]. Diminished self-esteem in Turner syndrome might be ameliorated by group cognitive-behavioral interventions [89]. Most importantly, a large population followed at the National Institutes of Health had higher educational and employment achievements than the general female population of the USA, although they were somewhat less likely to have married [90].

Undoubtedly, patients who travel to the National Institutes of Health form a special category, yet this is very reassuring information for all women with Turner syndrome.

CONCLUSION

As illustrated by the array of common and uncommon disorders experienced by people with Turner syndrome, both excellent medical care and scientific progress are served by follow-up in a longitudinal multidisciplinary setting. This should begin at birth, and continue through transition from pediatric to adult care and throughout the adult life span. At its annual meeting in 2014, the Turner Syndrome Society of the USA proposed a network of research centers (Turner Research Network) to be developed from existing Turner syndrome clinics (<http://www.turnersyndrome.org/#!professional-symposium/c1w49>). These Turner Research Network centers would promote compassionate sophisticated management, serve as a nexus for research of relevant issues, and also facilitate possible studies of involving therapy.

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Conflicts of interest

None.

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