Review Article

Cardiovascular Health in Turner Syndrome: Manifestations, Endocrine, and Metabolic Risk Factors with a look at Clinical Practice

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Abstract

Turner syndrome (TS) is the most frequent female chromosomal abnormality, with a higher overall mortality rate than the general population; cardiovascular events are a significant risk factor. Cardiovascular manifestations in TS include congenital heart diseases, in addition to acquired heart diseases such as acute aortic dissection, stroke, myocardial infarction, and hypertension. Growth hormone-insulin growth factor 1 axis abnormality, estrogen hormone deficiency, liability for diabetes mellitus, and dyslipidemia all are endocrine risk factors affecting cardiovascular health in TS. Heart anatomical defects should be closely monitored for progression and associated complications throughout the patient's lifetime by a skilled cardiologist.

Keywords: Endocrine, heart, Turner syndrome

Introduction

Turner syndrome (TS) is a condition in which all or a portion of an individual's cells lack the second sex chromosome. It is the most prevalent chromosomal defect in females, impacting one out of every 2500 live-born girls.[1] Short stature, ovarian dysgenesis, poor sexual development, cardiac and/or renal anomalies, low-set ears, webbed neck, and skeletal deformities including cubitus valgus, hearing difficulties, and susceptibility to ear infections are all common clinical characteristics of TS.[2] According to an observational study, TS patients had a three-fold higher overall mortality rate than the general population.[3] Cardiovascular events, which occur in 41% of patients, are a significant risk factor.[4]

Cardiovascular Manifestations in Turner Syndrome

Cardiovascular abnormalities are a major area of concern both during pregnancy and after birth. Fetal loss is believed to be 99% due to heart abnormalities that are not compatible with life,[5] whereas aortic coarctation and bicuspid aortic valve are more frequently occurring live birth defects.[6] Aortic aneurysms and dissections at a young age are associated with an increased risk of death later in life. Hypertension and diabetes mellitus are substantially more common among young adults than in the general population.[7] Cardiovascular manifestations of TS can be classified into the following:

Congenital heart diseases

Fetal sonography performed at gestational weeks of 11–14 is used to screen for TS in the early stages of pregnancy.[8] Nuchal translucency is common in karyotyping consistent with TS, and this fetal appearance is associated with a poor prognosis for fetal malformations, including cardiac and skeletal malformations.[9] Neck webbing is a postnatal manifestation of lymphedema in the lower neck region of patients with TS.

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Due to the association between this external characteristic and congenital heart disease (CHD) in TS,[10] a pivotal relationship between lymph buildup and CHD had been hypothesized.[5]

Types of congenital heart disease in Turner syndrome

CHD spectrum extends from minor simple defects to serious and extremely complex abnormalities; consequently, while some lesions are asymptomatic,[11] others are incongruous with a normal life span or even the survival of a fetus.[12] The type of research conducted, the range of defects assessed, and the karyotype distribution within the examined cohort all have an effect on the frequency of CHD that is reported. The increased early life death rate due to severe CHD may introduce selection bias into research achieved in adolescent years, as less severe cardiac phenotypes survive longer as individuals aged,[5] these cardiac defects include:

Bicuspid aortic valve

About 15%–30% of TS patients have a bicuspid aortic valve,[11] in comparison with 1%–2% of the general population.[13] Aortic valve anomalies of an instantaneous severity, such as aortic valve congenital stenosis or dysplasia, may occur infrequently in infants with TS.[14] In children, the outcomes of having a bicuspid aortic valve are optimistic, with the chance of related morbidity increasing with age.[13] Although few pediatric studies on aortic valve function in TS exist, adult TS females with bicuspid aortic valve have stenosis in 28%–46% of patients and regurgitation in 42%–50% of patients.[11] A critical and significant point for clinicians is that with bicuspid aortic valves, the yearly incidence of endocarditis in the overall population rises by 0.3%–2%;[13] therefore, because TS females are more likely to have bicuspid aortic valves, the probability of endocarditis must be higher in these women.[15]

Coarctation of the aorta

It is found in up to 17% of females with TS,[10,11] in comparison with 0.04% in the general population.[16] Coarctation of the aorta (COA's) severity in TS has gotten scant attention. The frequency with which COAs are repaired is 5%–12% in childhood and adulthood.[17] Furthermore, cardiac magnetic resonance (CMR) has revealed undetected COA in 5%–8% of patients.[11] Notably, correcting the coarctation may not eliminate the risk of aortic dissection, as dissections can occur even years after repair.[5]

Numerous congenital heart diseases can be found in patients with Turner syndrome, including the following

Ventricular septal defects are found in 1%–4% of TS patients, while atrial septal defects are present in 1%–2% of them,[14,18] on the other hand partial anomalous pulmonary venous drainage are present in 13%–15% of TS patients, persistent left superior vena cava (in 8%–13%).[19] Interrupted inferior vena cava and pulmonary valve stenosis are also congenital heart diseases reported in TS patients.[5]

CHD is detectable in both monosomy[10,11] and mosaic karyotypes,[5] demonstrating the diversity of CHD in TS. In addition, distinctive external morphological characteristics could be present or not to direct attention toward congenital heart defects, and there is not always a perfect match between exterior phenotype and congenital cardiac disease.[20]

Acquired heart diseases

With an elevated risk of acute aortic dissection, stroke, and myocardial infarction, these acquired heart diseases are the primary cause of mortality in TS.[21] Although acquired heart disease adds more to all causes of mortality as people get older, it can be hard to differentiate between congenital and acquired heart disease and numerous adverse features, including aortic dilation,[11] proarrhythmic traits,[22] and hypertension,[23] appear to be interrelated and persistent in TS.

Hypertension

Blood pressure is increased in TS patients of all ages.[24] Children and adolescents suffer from hypertension at a rate of 21%–40%,[23] whereas adults suffer at a rate of 50%–58%.[17] Hypertension impacted the diastolic, systolic, and pulse pressures with a blunted nocturnal dipping phase characteristic of TS.[23] Hypertension is linked to a considerable increase in morbidity and mortality,[12] and unfortunately, there is a high rate of nondiagnosis, with approximately only 4%–22% of patients receiving therapy.[24] No evidence exists to support the use of specific antihypertensive therapy in TS; hence, the therapeutic agent should be chosen based on general guidelines where blood pressure reduction is the primary target.[25]

Endocrine and Metabolic Risk Factors Affecting Cardiovascular Health in Turner Syndrome

Growth hormone deficiency or resistance

There is an unresolved inequity in the "growth hormone (GH)-insulin growth factor-1 and insulin growth factor binding protein" axis. This abnormality could be due to relative resistance to GH actions,[26] GH synthesis failure, or enhanced serum binding.[27] Some studies have reported that GH secretion, both spontaneous and induced, is reduced,[28] whereas others have revealed normal GH secretion.[29] Given this knowledge base on GH signaling in TS, as well as the fact that normal ultimate height can be achieved with supraphysiological dosages of recombinant human GH,[30] treatment should begin in infancy to allow for proper skeletal catch-up, and it should be stopped when the child reaches his or her final height or the point at which growth potential is exhausted.[31]

Excess GH, on the other hand, can produce calcifications in the mitral and aortic valves, arrhythmia, and hypertension.[32] Thus, there is a potential for serious cardiovascular effects when higher doses of recombinant GH are given over several years to young girls with TS, and it would be extremely beneficial to conduct forthcoming studies on metabolism and cardiovascular health in TS patients receiving recombinant human GH treatment.[5]

Estrogen deficiency

The adverse prognostic effect of declining ovarian function on cardiovascular health during normal menopause as well as premature ovarian failure demonstrates the importance of endogenous estrogen production by the ovaries for cardiovascular system function,[33] and thus, TS girls are at risk for this adverse effect due to estrogen deficiency.

Diabetes mellitus

Diabetes mellitus, Type 1 and Type 2, is more common in TS patients and adversely affects patients' cardiovascular health.[21]

Dyslipidemia

Patients with TS appear to have more atherogenic lipid profiles than those without TS, which appear to begin in childhood and progress through adulthood. Half of the adult females with TS have abnormally high total cholesterol, whereas one-quarter of them have abnormally low high-density lipoprotein (HDL) cholesterol.[34] According to a retrospective cohort study published recently, 27% of children and adolescents with TS were suffering from hypercholesterolemia recognized in their hospital medical records.[35] Carotid artery intima-medial thickness, which is a prognosticator of early atherosclerosis in young people with TS, correlates positively with low-density lipoprotein (LDL) cholesterol levels and negatively with HDL cholesterol levels.[36]

Diagnostic measures and management of cardiac diseases in TS and suggestions for clinical practice according to the American Heart Association

A fetal echocardiogram should be conducted if TS is strongly suspected or has been confirmed prenatally. If CHD is found, a pediatric cardiologist should be consulted and a multidisciplinary postnatal therapy plan should be done.

All newly diagnosed TS patients should be assessed by an expert cardiologist who is aware of the full range of cardiovascular disorders associated with TS. Additionally, they should experience the following evaluations:

- A thorough physical examination, including cardiovascular system assessment especially the measurement of femoral pulses and four extremities' blood pressures must be conducted.
- Even if a fetal echocardiogram and cardiac examination are normal, a thorough transthoracic echocardiogram (TTE) should be done because some cardiac defects may be undetectable on a fetal echocardiogram.
- TTE should be used to visualize the coronary arteries in infants, or computed tomography (CT) or cardiac magnetic resonance (CMR) in adults.

An electrocardiogram (ECG) should be performed to rule out any conduction abnormalities.[6]

Management

Patients with TS who have congenital heart problems should be managed by their cardiologist in collaboration with a multidisciplinary team. Persons without structural heart diseases should have their blood pressure checked annually, and clinical practitioners should be cautious in checking girls with TS for hypertension, and treat them according to general population standards. For those with normal-appearing aortas, periodic surveillance imaging is recommended. Finally, clinicians should refer to the American Heart Association's most recent guidelines for the prevention and treatment of infective endocarditis.[6]

Conclusions

TS individuals' cardiovascular systems may be compromised throughout their lives. Whether these comorbidities are age or karyotype related, every TS patient should have access to close monitoring for cardiovascular health. Early detection of endocrinopathies is critical for starting hormone replacement therapy, such as estrogen and GH therapy, and balancing the benefits and adverse effects for cardiovascular health, as well as defining the duration of therapy. Heart anatomical defects should be closely monitored for the progression of defects and associated complications throughout the patient's lifetime by a skilled cardiologist using repeated echocardiography and CT/magnetic resonance imaging.

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Conflicts of interest

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