Turner syndrome
Cardiovascular Disease from Womb to Tomb

Patient A
- 25 years old female referred for fetal evaluation because of fetal cystic hygroma. The fetal cardiac evaluation was done at 18 weeks’ gestation.
- At birth, the infant had dysmorphic features and lymphedema and was diagnosed with Turner syndrome.

Patient B
- 19 years old female patient with the diagnosis of Turner syndrome.
- She was born with unicuspid aortic valve with coarctation of the aorta.
- She had repair of her coarctation at the age of 3 years.
- She had been followed up with progressive stenosis of the aortic valve and dilatation of aortic sinus.

Definition Turner Syndrome
- The incidence is 5/1000 -1/2500 of live birth with estimated 10% incidence in spontaneously aborted fetus.
- The diagnosis is established with the combination of complete or partial absence of X chromosome and certain phenotypic features. The most severe manifestations are associated with 45,X genotype.
- The syndrome affects multiple systems and patients have increased all cause mortality.
- Today I will discuss the cardiac manifestation

Fetal Life
- The TS diagnosis is suspected in first trimester usually due to the presence of cystic hygroma.
- Cystic hygroma is significantly associated with congenital heart disease (60%).
- The presence of cystic hygroma and congenital heart disease are associated with anasarca and high risk of spontaneous miscarriage.

Fetal Life
- It is possible to diagnose the more severe cardiac conditions such as hypoplastic left heart syndrome (HLHS) during the first trimester, offering the family the option for early termination.
- Other anomalies such as coarctation and PAPVR are more challenging to diagnose in utero and can be missed.
- For such lesions, the diagnosis if made usually is suspected during the second trimester.
Fetal Cardiac Anomalies/ Theories

- Fetal jugular obstruction is thought to be responsible for the cystic hygroma and the congenital heart disease.
- The dilated lymphatics are thought to obstruct left sided lesions leading to BAV, Co Aorta and HLHS due to decreased flow.
- Specific right sided lesions mostly venous anomalies are thought to be secondary to back pressure from obstructed forward flow.
- Alternatively less accepted theories advocate parental imprinting and methylations as etiologic.

Fetal Cardiac Anomalies

- Accordingly, bi-allelic expression is essential for normal cardiovascular development.
- This specific gene however has not been identified.

After Birth/Congenital Anomalies

- Lesions that are not yet diagnosed during fetal life are usually picked up at birth.
- BAV incidence in TS is 10-30% depending on the series mostly due to right and left coronary leaflet fusion.
- High association between BAV and coarctation.
- High association between cardiac findings and web neck also with karyotype 45, X or the absence of X chromosome short arm.

Congenital Anomalies/ Pediatric

- Most coarctations that are missed during fetal life or suspected at birth are confirmed or ruled out within the first few weeks of life.
- Other arch anomalies included elongated and narrowed transverse arch, and aberrant right subclavian.
- Shunt lesion described included ASD.
- Venous anomalies included PAPVR is present in up to 3% of the cases.

Congenital Anomalies/ Pediatric

- Persistent left SVC to a coronary sinus was another venous anomaly described in Turner syndrome can be present in up to 13% of cases based on MRI data.
- Other rare anomalies such as congenital anomalies of the coronary including single origin and ostial narrowing have been described in case reports, the incidence or prevalence was not established.
Treatment: Surgical

- Many of these lesions require surgical repair.
- The timing and the type of surgery is dictated by the severity of the lesion.
- Patients with TS are offered complete repair similar to patients with normal karyotype.

Outcome: Surgical/Mortality

- TS patients with coarctation of the aorta and arch anomalies requiring surgery had similar mortality compared to non TS.
- Patients with HLHS had significantly higher mortality after repair compared to non TS patients (66% vs 89% after 1995).
- The mortality in HLHS was reported in more than one series.

Outcome: Surgical/Morbidity

- Increased morbidity was also noted in pediatric patients after surgical repair.
- Increased length of stay compared to non TS patients with comparable lesions.
- The specific causes could not be identified although prolonged respiratory support, poor feeding, and prolonged chest tube drainage were suggested.

Outcome: Surgical/Morbidity

- There is no literature to support that the rate of re-intervention after successful arch repair in TS exceeds the non TS patients.
- Balloon dilatation on native and operated sites has been successfully performed. There is however reports of increased complications with the intervention.
- Aneurysm formation and dissection were described with balloon dilatation and has been described even after stent placement.

After birth/Rhythm Disorder

- Increased incidence of prolonged QTc was diagnosed in patients with TS by EKG and confirmed by genetic testing, with the highest incidence in 45X karyotype. Ionic channel mutations were the most identified:
- SCN5A (3p.21) associated with LQT3 and Brugada, Na channel.
- KCNH2 (7q36.1) associated with LQT2, K channel.
- The role of prolonged QTc as etiologic in the increased mortality secondary to sudden death could not be established.

Outcome: Surgical/Morbidity

- Increased incidence of prolonged QTc was diagnosed in patients with TS by EKG and confirmed by genetic testing, with the highest incidence in 45X karyotype. Ionic channel mutations were the most identified:
- SCN5A (3p.21) associated with LQT3 and Brugada, Na channel.
- KCNH2 (7q36.1) associated with LQT2, K channel.
- The role of prolonged QTc as etiologic in the increased mortality secondary to sudden death could not be established.

Outcome: Surgical/Morbidity

- Increased incidence of prolonged QTc was diagnosed in patients with TS by EKG and confirmed by genetic testing, with the highest incidence in 45X karyotype. Ionic channel mutations were the most identified:
- SCN5A (3p.21) associated with LQT3 and Brugada, Na channel.
- KCNH2 (7q36.1) associated with LQT2, K channel.
- The role of prolonged QTc as etiologic in the increased mortality secondary to sudden death could not be established.

Outcome: Surgical/Morbidity

- Increased incidence of prolonged QTc was diagnosed in patients with TS by EKG and confirmed by genetic testing, with the highest incidence in 45X karyotype. Ionic channel mutations were the most identified:
- SCN5A (3p.21) associated with LQT3 and Brugada, Na channel.
- KCNH2 (7q36.1) associated with LQT2, K channel.
- The role of prolonged QTc as etiologic in the increased mortality secondary to sudden death could not be established.

Outcome: Surgical/Morbidity

- Increased incidence of prolonged QTc was diagnosed in patients with TS by EKG and confirmed by genetic testing, with the highest incidence in 45X karyotype. Ionic channel mutations were the most identified:
- SCN5A (3p.21) associated with LQT3 and Brugada, Na channel.
- KCNH2 (7q36.1) associated with LQT2, K channel.
- The role of prolonged QTc as etiologic in the increased mortality secondary to sudden death could not be established.

Outcome: Surgical/Morbidity

- Increased incidence of prolonged QTc was diagnosed in patients with TS by EKG and confirmed by genetic testing, with the highest incidence in 45X karyotype. Ionic channel mutations were the most identified:
- SCN5A (3p.21) associated with LQT3 and Brugada, Na channel.
- KCNH2 (7q36.1) associated with LQT2, K channel.
- The role of prolonged QTc as etiologic in the increased mortality secondary to sudden death could not be established.
Rhythm disorder

- Additionally, increased intrinsic heart rate, and increased incidence of supraventricular tachycardia (SVT) have been reported in TS.
- Study of heart rate variability suggested deterioration of both sympathetic and parasympathetic components of the autonomic system indicating a component of autonomic dysfunction.

Additional Reading:

Acquired Heart Disease/ Aortopathy

- By adulthood, 50-70% of patients have abnormalities in the aorta, and proximal part of the head and neck vessels.
- These included in addition to the congenital anomalies, dilatation of the thoracic and abdominal aorta, aortic sinus dilatation, ascending aorta dilatation in addition to the dilatation of the proximal branches including the carotids.

Additional Reading:
- Mortensen KH et al. Abnormalities of the major intrathoracic arteries in Turner syndrome as revealed by magnetic resonance imaging. Cardiol Young. 2010 Apr;20(2):191-200

Aortic valve and Ascending

Aortopathy/ Diagnosis

- The MRI findings gave evidence of generalized aortopathy in TS involving the aorta and the branches and remains the gold standard for diagnosis.
- It is recommended that the first MRI be done when the patient is old enough to avoid sedation so 8-10 years of age and if negative repeated every 5-10 years in the absence of other risk factors.
- If positive then it should be repeated yearly.

ECHO Limitation

- Echocardiogram alone is insufficient. Although it is an excellent tool for diagnosis of intracardiac structures, MRI provides better delineation of extracardiac vascular structures especially in older patients.
- MRI has the ability to demonstrate the whole aorta and branches, a quality deficient in echocardiogram.

Aortopathy/Pathology

- The pathology of the aortic dilatation is medial cystic necrosis found in the aortic aneurysms.
- The pathophysiology for aortic dilatation has not been delineated.
- There is suggestion that it is expressed through transforming growth factor β (TGFβ) pathway similar to Marfan and Loeys-Dietz syndromes, however this remains a research question at this point.
- The process is thought to involve the whole arch.
Aortopathy/ Treatment

- The most common location for the dilatation in TS is the ascending aorta whereas it is the aortic sinus in Marfan and Loeys-Dietz syndromes.
- Longitudinal studies have also failed to show rapid rate of progression in aortic dilatation in TS as is seen in Marfan and Loeys-Dietz syndromes. Hence, the rate of growth cannot be used as an outcome measure.
- The benefits of medications including beta blockers and angiotensin receptor blocker ARB to slow progression as used in Marfan are not routinely indicated and remain to be studied.

Aortopathy/ Treatment

- There was no cardiac side effects noted with growth hormone supplementation.
- There was no change in the ascending or descending aorta dilatation.
- There were reports of improved aortic distensibility with growth hormone treatment.

Aortopathy/ Challenges

- Defining aortic dilatation is challenging in TS because of the patient small surface area. 33% of TS patients with absolute ascending aorta of 35 mm which is a normal size in adults dissected within 3 years.
- Proposed method is to use an indexed value ASI defined as absolute ascending aorta size/surface area.
- Patients with ASI of 2.0/m2 are at high risk of dissection hence require close follow up and those with 2.5/m2 at very high risk (27% dissection in 3 years).
- There were reports of improved aortic distensibility with growth hormone treatment.

Aortopathy/ Challenges

- Hence patients with ascending aorta of 2.5cm/m2 should be considered for aortic root replacement as a preventive therapy.
- Other methods to define ascending aorta dilatation such as the ratio of ascending to descending aorta >1.5 are less accurate.
- 33-50% of women with TS would meet the criteria for dilatation.
- This criteria also missed patients with dissection.

Aortopathy/ Dissection/ Epidemiology

- 10% of all dissections in TS occur in patients with no known risk factors.
- Average age of dissection for women was 31 years. 50% did not survive the event.
- The occurrence of dissection was less common than in Marfan and Loeys-Dietz syndrome at 1.4% in a Danish population based study.
Dissection/ Risk Factors

- Age: increase incidence with advancing age with a peak in incidence between the ages of 20-40 years and a mean age of 31 years.
- Karyotype: XO karyotype is associated with more severe phenotype
- Congenital heart disease: Most dissections occurred in patients with known risk factors such as BAV, Co aorta. Such events usually occur at young age second or third decade.
- Pregnancy.
- Hypertension has been implicated as a risk factor for dissection however the data is mixed, and more research is needed.
- Hypertension has been positively correlated with progressive aortic dilatation. Aggressive blood pressure control is recommended in TS patients both systolic and diastolic.

Pregnancy in Turner Syndrome

- Although spontaneous pregnancy is possible in TS, most of the pregnancies are assisted with oocyte donation or frozen oocyte. Hence, these women are under close monitoring.
- Mortality has been estimated up to 2% mostly related to aortic dissection in pregnant patient with TS based on a survey of centers undergoing in vitro fertilization with oocyte donation conducted in USA.
- More significantly in that survey was that up to 50% of TS women undergoing the process did not have cardiovascular screening.
- Approximately 40% of women reported normal after evaluated by cardiologist not familiar with TS were found to have cardiovascular abnormalities that preclude pregnancy when evaluated by cardiologist familiar with the syndrome.

Pregnancy/ Management

- The American Society for Reproductive Medicine recommends:
  - Treatment of hypertension
  - Routine evaluation by cardiologist including echocardiogram
  - Attempt vaginal delivery if aortic root less than 40mm
  - Scheduled C-section for baseline or progressive aortic root dilatation during pregnancy
  - Pregnancy is contraindicated in patients with ascending aorta ASI of 2 cm/m2
- Adult TS/ Morbidity/CAD
- Carotid intimal thickening was abnormal in TS negatively influenced by age, metabolic risks, blood pressure and short duration of hormone therapy
- Abnormal aortic distensibility was also described.
Morbidity/ CAD

- Increased incidence of coronary artery disease with peak in 5th decade of life.
- Multifactorial etiology related to hypertension, premature ovarian failure, atherosclerotic burden, hyperlipidemia, obesity, diabetes, and hypercoagulability all of which are increased in adults with TS.
- Anomalies of the coronaries have been reported including dilatation of the coronaries.


Morbidity/ Cerebrovascular Accidents

- Incidence of stroke is increased in TS starting from second decade.
- The etiology is not well studied but proposed associations included the increased atherosclerotic load, the dilated proximal carotids, the increased intimal thickness.

Morbidity/ Hypertension

- Affects 25% of adolescents and 40-60% of adults.
- Abnormal autonomic tone has also been described.
- Systolic blood pressure is usually affected especially absence of the nocturnal drop.


Morbidity/ Hypertension

- The hypertension has been related to increased renin activity.
- Essential hypertension accounts for the majority of the causes. Renal and cardiac causes have been implicated and should be ruled out.

Turner Syndrome/Mortality

- British study looked at 3622 patients with Turner diagnosed by karyotype (1959-2002).
- Mortality is 3x higher than general population for all cause mortality.
- This increase is present in all age groups but particularly in adult population.
- Cardiac causes heavily contributed and included both the congenital and acquired diseases.

Plan for follow up

- At birth: Obtain cardiology consultation.
- If no congenital anomalies are present, routine evaluation every 5 years with echocardiogram. MRI/MRA of the aorta should be added starting at the age of 9-10 years then repeated every 5 years.
- Early cholesterol screening and repeat evaluation every 5 years.
- Focused discussion about cardiac risk factors in the preteen years with emphasis on avoiding added risks such as cigarette smoking.
- Rigorous diagnosis and control of hypertension.
- Thorough evaluation in patients contemplating pregnancy including an MRI/MRA of the aorta and branches.

Plan for follow up

- If aortic dilatation develop restrict contact sports and isometric exercise and change follow up to yearly.
- Patients with cardiac lesions have to be followed up more closely depending on the lesion.
- Incorporated within this follow up should be a plan to address modifiable risk factors for CAD, control of hypertension and pregnancy evaluation.

Patient A

- Was found to have abnormal aortic arch, LSVC to coronary sinus and BAV

Patient A Course

- Closed her ductus in the immediate neonatal period but the aortic arch was not obstructive.
- At the age of 3 years she still had no evidence of coarctation.
- She had a cholesterol screen at the age of 3 years which was normal
- She was seen yearly and the mother knew that an MRI will be done when she can lay still

Patient B

- Cardiac cath was done to evaluate for balloon dilatation vs surgical repair
- Cath confirmed moderate aortic stenosis and significant dilatation of the aortic sinus, but also showed mild narrowing of the left coronary artery which had a tangential course to the dilated sinus.

Patient B

- Balloon dilatation was not done because of the aortic sinus and the coronary anomaly.
- The patient underwent aortic root placement with coronary reimplantation and augmentation.
- The post operative course was complicated by severe intractable hypertension that required both beta blocker (Toprol) and angiotensin receptor blocker (losartan).
- She developed intestinal obstruction 10 days postoperatively and underwent surgical treatment.
- She was discharged home after prolonged recovery course.
Conclusions

- Turner syndrome is a multisystem disorder with increased overall mortality and morbidity mostly related to cardiac disease.
- Decreased awareness of the spectrum of cardiac complications in this disorder is prevalent among practitioners and cardiologists.
- Even patients with normal cardiac findings at birth will require lifelong follow up and evaluation by cardiologist experienced in Turner syndrome.
- Adult patients with Turner syndrome are best served in a setting of adults with congenital heart disease care expertise where acquired and congenital aspect of the disease are addressed in addition to aggressive control of CAD risk factors.
- Aggressive control of the common cardiovascular risk factors and the risk factors specific to this disease is mandatory to decrease adult mortality and morbidity.