Turner Syndrome: Seeing the Whole Girl, Not Just the X

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• Dr. Connor has no conflicts of interest to disclose.
Learning Objectives

• TLW describe the care, including surveillance, for a child with Turner syndrome.

• TLW will describe the care, including surveillance, for an adolescent with Turner syndrome.

• TLW will describe the methods available to initiate and support pubertal development in the girl and adolescent with Turner syndrome.

The ABC’s of Turner Syndrome

• Audiology
• Autoimmunity
• Cardiac defects
• Dermatologic manifestations
• Failure to grow
• Gastrointestinal disease
• Genetics
• Metabolic disorders
• Orthopedic complications
• Psychosocial manifestations
• Renal abnormalities
• Reproductive and pubertal disorders
• X-linked disorders
Disclosures

• Dr. Connor has nothing to disclose.

Turner Syndrome

Time of diagnosis:

• 20-30% dx in neonatal periods

• 35% as children short stature

• 30% as adolescents/adult women with primary amenorrhea, delayed puberty
The X Factor

- The X chromosome: contains near 1000 genes; 5% of total DNA in cells.

- In 46 XX individuals, one of the X chromosomes is randomly inactivated.

The X Chromosome

- Short arm = p
  - Genes on p arm = SHOX gene

- Long arm = q
  - Genes on q arm = gonadal function
Genetics of Turner Syndrome

• Absence of or structural abnormality of one copy of the X chromosome, often due to nondisjunction.

• Sporadic condition, not related to advanced maternal age. More often (70%) “missing” paternal sex chromosome.

Turner Syndrome
Absence of or structural abnormality of one copy of the X chromosome

• Haploinsufficiency-a condition that arises when the normal phenotype requires the protein product of both alleles, and reduction of 50% of gene function results in an abnormal phenotype.

• i.e. SHOX gene-present on both X and Y chromosome, when missing part of SHOX gene (i.e. Turner Syndrome), leads to short stature.
Postnatal Outcomes

• Half are pure monosomy 45 X karyotype
• Half are mosaic—
  – Degree of mosaicism does not correlate with phenotype
  – 46XX/45 X;
  – 46 X, del (Xp)—short arm missing
What about the Y?

- 46 XY/45 X: found in 6-11%
- Variable presentation: clitoromegaly vs ambiguous genitalia vs descended testes.
- Need to assess for gonadoblastoma. 12% risk, even at a young age.
- One study: prevalence of germ cell tumors 18/119 (15%) (Cools et al, Endo Rev 2006)

Postnatal Diagnosis

- Peripheral leukocytes karyotype with minimum of 30 cell count. Identifies 10% mosaicism by 95% confidence.
- If blood tests normal, but strong clinical suspicion—tissue sample.
- Test for Y with the use of FISH/PCR for the patient with ambiguity; or if a marker chromosome is present (sex chromosome fragment of unknown origin).
- Routine testing for SRY or Y in 45 X without masculinization is not clinically warranted. (Turner Guidelines-)

Zhong and Layman, Fertility and Sterility 2012
Short stature: average of 20 cm shorter than peers
- IUGR
- Slowed childhood growth
- Mild skeletal dysplasia—Upper to Lower ratio
- Lack of pubertal growth spurt
Growth Hormone and Turner Syndrome

- GH FDA approved for Turner Syndrome in 1996.
- Standard of care to consider growth hormone as soon as evidence of decreased linear growth velocity.
- Best outcomes with younger age of initiation, higher dosing, longer duration of therapy.
- Height “gain”: 7-18 centimeters. (Canadian Growth Hormone Advisory Committee, JCEM 2005, Davenport, JCEM 2010)
Safety of GH in Turner Syndrome

- Intracranial hypertension
- Slipped capital femoral epiphysis
- Scoliosis—worsening of underlying risk
- Recommend following IGF-1, glucose and glucose levels (increased risk of insulin resistance)
- No evidence of adverse effects on cardiac factors (i.e. increased aortic diameter)

Adjunct therapy

Oxandralone

- Nonaromatizable (does not get converted to estrogen) anabolic steroid.
- Promotes growth independent of GH.
- Studies show increase in growth velocity and increase in final adult height of 2-4 cm.
- Side effects: virilization, cliteromegaly, deepening voice which is dose dependent (0.03 mg/kg vs 0.06 mg/kg).
TS and the Heart

Most Serious and Life Threatening Complications
Bicuspid Aortic Valve (BAV)
• Affects 30% of those with TS (vs 1-2%)
• Risk of morbidity increases with age.
• Risk of premature valvular stenosis—accelerated by calcification. 26-48% of adults with TS with BAV.

Bicuspid Aortic Valve (BAV)
• Risk of valvular regurgitation—42-50% of adults with TS and BAV. Promotes aortic dilatation.
• Risk of aortic wall abnormalities-dilation, aneurysm, dissection.
• Risk of endocarditis.
Coarctation of the Aorta

- 12-17% of those with TS (vs 0.04%)
- Associated with BAV.
- Abnormal aortic phenotype.
- Surgical repair—patch angioplasty, balloon or stent repair.

Other less common congenital defects:

- ASD, VSD, Pulmonary valve stenosis
- Cardiac lesions seen in both monosomy and mosaicism.
Cardiac-electrocardiographic conduction abnormalities

- Sinus Tachycardia-increased conduction through the atria and AV node-leads to increased risk of atrial tachycardia.
- Prolonged QT: 36% of children, 21% of adults. (Bondy et al, Pediatrics 2006)
- Be aware before prescribing certain medications: CNS Stimulants, some antibiotics, antidepressants

Aortic Dissection

- 1-2% TS. 100-fold increased risk.
- Peak incidence in third to fifth decade.
- 22% die before getting to hospital.
- Accounts for 8% of all deaths in those with TS.
- Descending aorta better prognosis than ascending.
Risk Factors for Dissection

- **Congenital Heart Lesion**: 87-95% of those with dissection have history of BAV or Coarc.
- **Hypertension**: affects 25% of adolescents with TS, and up to 50% of adult women; loss of diurnal drop in BP.

Risk Factor for Dissection

- **Aortic Dilatation**: affects 19% of children and adolescents with TS and can start from 6 years of age
- **Measurement**:
  - young children: echocardiography
  - Older adolescents: MRI normalized to BSA to give the aortic size index (ASI)

Treatment: Address modifiable factors, more frequent monitoring, counsel on signs of dissection, surgical consult.
Hypertension Therapy

- Lifestyle changes, discuss smoke exposure;
- RX: angiotensin receptor blocker (ARB) at the lowest available dose.
- ARBS-SE: dizziness, headache, cough, Class C/D for pregnancy.

Risk Factors for Dissection

- Pregnancy-risk for dissection 2 in 100 pregnancies with TS
- In 7 cases of aortic dissection reported after assisted reproductive technologies (ART), 6 patients died (Turtle EJ, et al, Arch Dis Child 2015)
- Practice Committee of ASRM “Turner syndrome is a relative contraindication for pregnancy, and patients should be encouraged to consider alternatives”
Other Acquired Vascular Disease

- Strokes-increased from the second decade of life. Risk factors: HTN, insulin resistance, visceral obesity; atrial fibrillation.
- Cardiovascular disease—higher with visceral obesity, insulin resistance.

Guidelines for TS and Cardiac

- Initial evaluation by cardiologist
- BP of all 4 extremities
- Imaging: ECHO for younger children, MRI for older adolescents and adults.
- ECG
- Follow up: BP, Reevaluation with imaging-MRI at age able to cooperate and then every 5-10 years. Manage hypertension.
Puberty and Reproduction

- Age to initiate estrogen
- Estrogen formulations
- Goals of pubertal initiation
- Introduction of progestin
Fertility

- Statistics
- Considerations for conception
- Ethical concerns
Autoimmunity

- Autoimmune thyroiditis
- Rheumatoid Arthritis
- Celiac disease
- Inflammatory Bowel Disease
- Hypophysitis

Metabolic Disorders

- Insulin resistance
- Type 2 diabetes
- Hyperlipidemia
- Hepatic steatosis
Neuropsychiatric Issues

- Anxiety
- Visual Spatial differences
- Mathematics
- Social recognition

TS and Renal Disease

- Congenital anomalies: 30-40% of patients with TS
  - Collecting system malformations- 20%
  - Horseshoe kidney – 10%
  - Other - 5%
- Monitor for urinary tract infections and hypertension
- Guidelines: all should have baseline renal ultrasound
TS and the Ear

• Conductive Hearing loss—frequent due to abnormal anatomy and increased risk of otitis media.
  – Aggressive management of OM, middle ear effusion, early referral to ENT
• Progressive sensorineural hearing loss as adults

Guidelines: Baseline assessment by audiologist at diagnosis, then every 1 to 3 years based on history of disease.

Gastrointestinal Problems

• Elevated liver enzymes
• Lymphangiectasia
Dermatology

- Nevi --- multiple pigmented, halo
- Keloid and hypertrophic scar formation
- Multiple pilomatrixoma
- Pustular psoriasis
- Vitiligo

Orthopedic Diagnoses

- Scoliosis
- Leg length
- Knee
- Feet
Other Diagnoses

• Must keep in mind X-linked diagnoses, including but not limited to
  – Hemophilia
  – Duchenne muscular dystrophy
  – Color blindness
References

• Chacko et al. Endocrinol Metab Clin N Am 2012 41;713-734. “Update on Turner and Noonan Syndromes”
• Mavinkurve and O’Gorman. BBA Clinical 3. 2015;304-309. “Cardiometabolic and vascular risks in young and adolescent girls with Turner syndrome”

Website Information

• www.turnersyndrome.org
• www.turnersyndromefoundation.org