Turner Syndrome (45,X)

Lauren Lee
Guest Speaker: Kayla Gray
Medical Genetics Presentation
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Section #1

Introduction to Turner Syndrome:

- Defining TS
- Disease Discovery
  - Clinical & Lab Diagnosis
- Clinical Reports
- Important & Unique Features

What is Turner Syndrome (TS)?

- It is a chromosomal abnormality in which all or part of one of the sex chromosomes is absent, affecting female development.
  - Unaffected humans have 46 chromosomes, of which two are sex chromosomes
  - Normal females have two X chromosomes, but in TS, one of those sex chromosomes is absent or has other abnormalities
  - In some cases, the chromosome is missing in some cells but not others, a condition referred to as mosaicism
- Although it is relatively common at conception and in spontaneous abortions, the incidence in liveborn female infants is estimated around 1:5,000 to 1:10,000.

Disease Discovery:

- 1938: Henry Turner first described Turner Syndrome, one of the most common chromosomal abnormalities.
- 1954: The absence of a Barr body, along with the absence of one x chromosome was discovered
- 1959: Cytogenetically confirmed

- Turner syndrome is caused by the absence of one set of genes from the short arm of one X chromosome (monosomy).
- In patients with 45,X karyotype, about two thirds are missing the paternal X chromosome.

Clinical & Lab Diagnosis:

Prenatal Diagnosis:

- Turner syndrome may be suspected in pregnancy during an ultrasound test but must be confirmed by prenatal testing - chorionic villous sampling or amniocentesis
- If a diagnosis is confirmed prenatally, the baby may be under the care of a specialist pediatrician immediately after birth.

Clinical & Lab Diagnosis

Postnatal Diagnosis:

- A diagnosis of Turner syndrome may be suspected when there are a number of typical physical features observed such as webbed neck, a broad chest and widely spaced nipples.
- Sometimes diagnosis is made at birth because of heart problems, and unusually wide neck or swelling of the hands and feet.
- Many girls are diagnosed in early childhood when a slow growth rate and other features are identified. Diagnosis sometimes takes place later when puberty does not occur.

Diagnosis is confirmed by a blood test (karyotype). This is used to analyze the chromosomal composition of the female.

Relevant Reports for Prognosis

- No known ethnic or racial factors influence frequency
- 99% of conceptions are thought to result in spontaneous abortion or stillbirth
- Approximately 15% of all spontaneous abortions have the X,O Karyotype
- Prevalence of cardiovascular malformations ranges from 17% to 45% (different Karyotypes)
- The higher prevalence is seen in those who exhibit the pure 45,X monosomy
  - This is due to the most common cardiovascular malformations:
    - aortic valve abnormalities
    - coarctation of the aorta.

Bicuspid Aortic Valve Malformation

- Up to 15% of adults with Turner Syndrome have bicuspid aortic valves. This means that there are only two parts to the valves in the main blood vessel leading to the heart (instead of three)
- The fear is that although bicuspid valves are essentially functional, later failure is more likely to occur.

Coarctation of Aorta

- Between 5% and 10% of those born with Turner Syndrome are affected
- This is a congenital narrowing of the descending aorta
- Always suggests the need for further tests when recognized

Important & Unique Features:

- Short staure (normal first 3 years of development, but does not experience normal growth or growth spurt during puberty)
- Non-functioning ovaries
- Infertility
- Frequent ear infections during early childhood which may result in loss of hearing
- Usually have normal intelligence with good verbal and reading skills

Section #2

Clinical Features:

- Important clinical phenotypes
- Additional risks/features
- Causes/Mode of inheritance

Important Clinical Phenotypes

Observed at birth:

- An especially wide neck (webbed neck) and a low or indistinct hairline.
- Swelling of hands and feet

Observed during growth:

- A short stature
- A broad (shield-shaped) chest and widely spaced nipples.
- Arms that turn out slightly at the elbow.
- Hyperconvexed nails

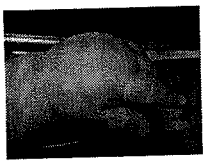
Additional Risks/Features

- A heart murmur, sometimes associated with narrowing of the aorta
- A tendency to develop high blood pressure
- Minor eye problems that are corrected by glasses.
- Scoliosis occurs in 10% of adolescent girls
- The thyroid gland becomes under-active in about 10% of women who have TS. Regular blood tests are necessary to detect it early and if necessary treat with thyroid replacement

Additional Risks/Features

- Older or over-weight women with TS are slightly more at risk of developing diabetes.
- Osteoporosis can develop because of a lack of estrogen
- Approximately one-third of all women with TS will have one of three kidney abnormalities
- High arched palate/ dental crowding

Clinical & Lab Diagnosis



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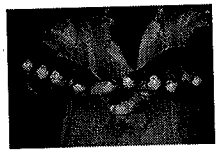

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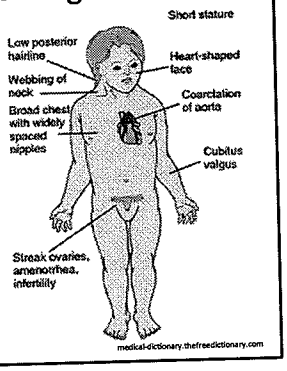


medical-dictionary.thefreedictionary.com

Causes/Mode of Inheritance

- Since the mutation is on the X chromosome, it is considered an X-linked disorder
- It is neither considered dominant nor recessive because it is not a true sex-linked disorder
- There is no true inheritance pattern for Turner Syndrome because it is a random occurrence.
- However, a female can manifest an X-linked recessive disorder by being a carrier of an X-linked recessive mutation and having only a single X chromosome.
- It is caused by nondisjuction (failure of distributing chromosomes during meiosis)

Section #3

Diagnosis, Treatment & Disease Management

- Modern methods in disease diagnosis
- Current treatment methods
- Genetic risk
- Community support groups

Modern Methods in Disease Diagnosis

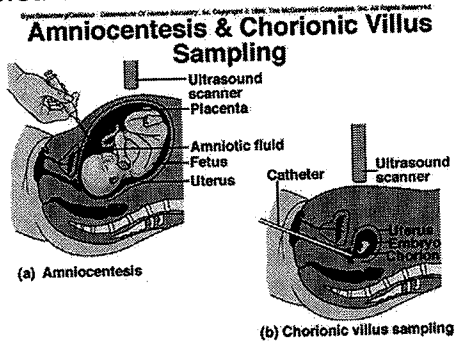
- Ultrasound→Amniocentesis, Chorionic villous sampling
- A standard 30 cell Karyotype is needed for diagnosis of TS in order to exclude mosaicism.
- Diagnosis is confirmed by the presence of a 45,X cell line or a cell line with deletion of the short arm of the X chromosome (Xp deletion)
- Thyroid function tests
- TSH measurements should be taken and repeated every 1-2 years
- Urinanalysis for glucose for those taking HGH
- Ultrasonography of kidneys and renal collecting system
- echocardiography/MRI exam of heart and aorta
- Measure bone density
- Hearing assessment/ follow-up evaluations

Testing for Y Chromosome

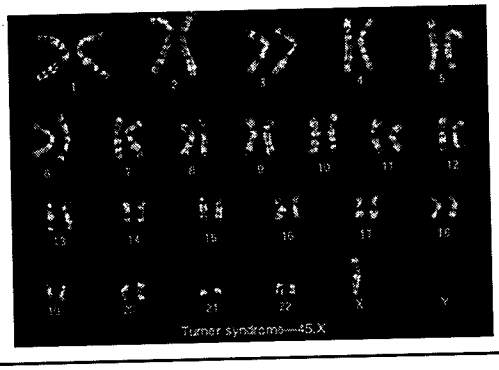
Virilization: Signs of excess androgens are generally absent.

If virilization occurs, a search for Y chromosomal material by fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) is necessary as part of an evaluation for possible gonadoblastoma.

Methods Used for Prenatal Diagnosis



Methods Used for Diagnosis



Current Treatment Methods

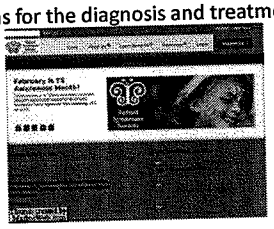
- Pediatric endocrinologist
- Growth hormone injections
  - Average adult height: 4'7"
- Estrogen replacement therapy
  - Begins at time of puberty
  - Promote healthy womb and prevent osteoporosis
- Cardiologist assessments if needed
- Routine health maintenance visits
- Reproductive technologies
  - Pregnancy with donor embryos

Genetic Risk

- Advanced maternal age is not associated with an increased incidence in TS
  - "In each subsequent pregnancy, the chance of having another baby with Turner syndrome would not be increased over the maternal age risk for chromosome abnormalities that affects every woman."
    - Lucile Packard Children's Hospital
- If using implantation, uterine factors increase risk for miscarriage

Community Support

- Turner Syndrome Society of the U.S.
  - Country-wide non-profit organization to provide health-related resources to patients, families and physicians for the diagnosis and treatment of TS



Section #4

Conclusion

- Absent of entire/short arm of X chromosome (45,X)
  - Only occurs in women (at random)
- Incidence is low, mostly resulting in miscarraige
  - Affects phenotype but usually of normal intelligence
- Advances in technology assist with diagnosis, treatment and management of TS

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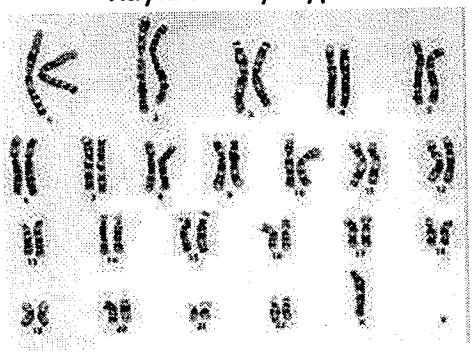
Kayla's Karyotype



Multiple Choice Questions

Name: Lauren Lee Presentation on: Turner Syndrome

1. Individuals with Turner Syndrome have 45 chromosomes (one sex chromosome is missing in the cells of these "XO" individuals). This usually is caused by meiotic nondisjunction during gametogenesis. Which statement is NOT correct concerning people with this disorder?
    a. They are genetic females
    b. They are subject to sex-linked disorders at frequencies similar to those predicted for normal females
    c. The nondisjunction event could have occurred during meiosis in either male or female parent
    d. If meiosis occurs in Turner Syndrome individuals, one daughter cell resulting from the first meiotic division will have no sex chromosome.

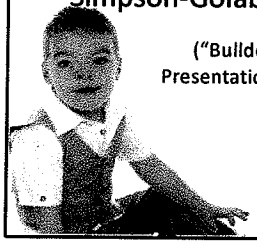
2. A human with Turner Syndrome would represent:
    a. A diploid condition
    b. A euploid condition
    c. An aneuploid condition
    d. A trisomic condition

Sera McNutt

4/12/2012

Simpson-Golabi-Behmel Syndrome

("Bulldog Syndrome")
Presentation by Sera McNutt



Discovery

- Simpson 1975
  - Two male cousins with distinctive facial appearance including a protruding jaw, flat nasal bridge, enlarged tongue; broad, stocky appearance including broad, short hands with short fingers.
  - Intelligence normal
  - Laboratory tests confirmed that this was not a disease that was previously described
- Golabi 1984 and Behmel 1984 (separately)
  - Described 15 males (many of them related) with similar features as described by Simpson plus extra ribs, gastrointestinal malformations, and extra nipples
  - Female carrier mothers expressed features more mildly
  - Concluded that it was the same disease as described by Simpson

Discovery continued...

- Once these 3 scientists gave this disorder a name, past cases that were previously labeled as mysteries were able to be diagnosed
  - In 2011 Gurrieri determined that the first reported case was actually that of an infant child in 1940.
- Reports:
  - Behmel, A., Plochl, E., Rosenkranz, W. A new X-linked dysplasia gigantism syndrome: identical with the Simpson dysplasia syndrome? Hum. Genet. 67: 409-413, 1984. [PubMed: 6490008, related citations] [Full Text: Pubget]
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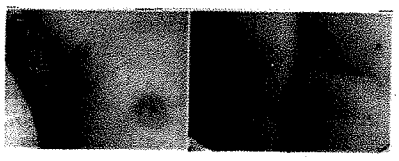
  - Golabi, M., Rosen, L. A new X-linked mental retardation-overgrowth syndrome. Am. J. Med. Genet. 17: 345-358, 1984. [PubMed: 6538755, related citations] [Full Text: Pubget]

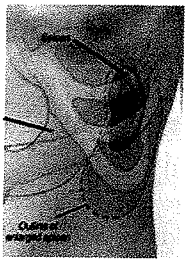
Phenotype - external

- General overgrowth (pre- and postnatal)
- Widely spaced eyes
- Low muscle tone
- Short nose, broad nasal bridge
- Large mouth and tongue with cleft palate
- Teeth don't align properly
- Extra nipples, undescended testicles.
- Hands
  - Polydactyly, small nails, short fingers, broad hands



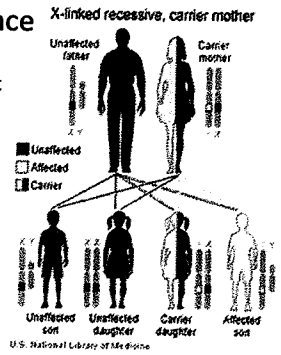
Phenotype - internal

- Enlarged organs especially kidneys, spleen, and liver
- Sometimes kidney cysts
- Increased risk of tumor development
- Possible digestion issues
- Extra ribs
- Heart defects
  - If present usually results in death before age 2
  - 50% diagnosed males die in newborn stage due to this



Mode of Inheritance

- Described cases consist of males only
- Males of the same family both diagnosed with the disease are connected by female carriers
- X-LINKED RECESSIVE
- Incidence unknown
  - 130 cases reported world-wide

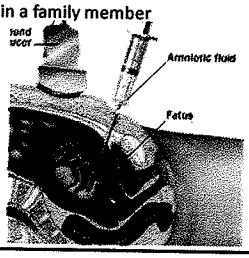


Diagnosis

- Cytogenetic
  - Caused by microdeletions in two genes present on X c'some
  - SGBS Type 1: GPC3 gene at Xq26.2
    - Exact function of gene unknown
  - SGBS Type 2: CXORF5 gene Xp22
    - Usually results in more severe phenotype
  - Severity of symptoms can depend on the size of the deletion
  - Detected by exon-specific PCR and Southern blot

Prenatal Diagnosis

- Genetic testing though amniocentesis or chorionic villus (placental tissue) sampling
  - FISH or PCR
  - Usually only done if a GPC3 mutation has already been identified in a family member



Genetic Risk

- Females who have been identified as carriers have a 25% chance of having a son with SGBS.
- Female carriers have 25% of having a daughter who is a carrier of the mutation.
- Men with the mutation have a 100% chance of having a daughter that is a carrier and a 0% chance of passing the mutation to a son.

Treatment

- Some individuals may require surgery to reduce tongue size to aid in speech development.
- Speech therapy to help with oral malformations
- May benefit from social support in order to increase self-esteem which may be low due to their unusual appearance
- May benefit from ultrasounds of abdomen (especially the kidneys) to check for cyst and tumor development.

Support Groups

- AmeriFace:
  - "The mission of AmeriFace is to provide information and emotional support to individuals with facial differences and their families and increase public understanding through awareness programs and education."
  - http://www.ameriface.org/

ameriface the cleft/craniofacial advocates

Support Groups

- NORD (National Organization for Rare Disorders)
  - dedicated to helping the nearly 30 million Americans with rare diseases, and the organizations that serve them, through programs of education, advocacy, research, and patient services.
  - Also allows patients with rare disorders to connect with one another for support.
  - http://rarediseases.org/

NORD
National Organization for Rare Disorders

Conclusion

- Simpson-Golabi-Behmel Syndrome is an X-linked recessive disorder initially described in 1975 and usually associated with a microdeletion of GPC3 gene on the q arm of X chromosome.
- Phenotype includes overgrowth, widely-spaced eyes, small nose, cleft lip or palate, extra nipples, large tongue and mouth, low muscle tone
- Most diagnosed patients can lead a normal life but may require monitoring for tumors, emotional and genetic counseling, and/or speech therapy

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Sara McNutt

Simpson-Golabi-Behmel Syndrome

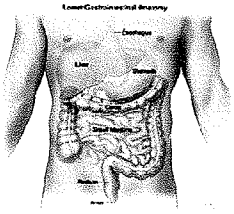
Multiple Choice Questions

1. Simpson-Golabi-Behmel syndrome is a disease predominantly found in males. What genetic mutation leads to the MOST severe cases of SGBS?
    a. Microdeletion of GPC3 gene on the X chromosome
    b. Microdeletion of GPC3 gene on the Y chromosome
    c. Deletion of CXORF5 gene on the X chromosome
    d. Microdeletion of GPC3 gene on chromosome 11
2. The most life-threatening phenotype of SGBS is _____ which results in the death of 50% of newborns with SGBS.
    a. Enlarged spleen
    b. Kidney cysts
    c. Tumor development
    d. Heart Defects

Answers:

1. C
2. D

Colon Cancer



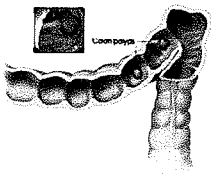
Morgan Zegers

Introduction

- Colon cancer is cancer of the large intestines.
- Fourth most common cancer in both men and women.
- One of the most common inherited cancer syndromes.
- Inherited gene defects that cause colon cancer are responsible for 5-10% of cases.
- Risk of developing colorectal cancer is about 1 in 20
- Two genetic syndromes increase the risk of developing colon cancer:
  - Familial adenomatous polyposis (FAP)
  - Hereditary nonpolyposis colorectal cancer (HNPCC), also know as Lynch syndrome

History

- Chinese recognized and treated colon cancer nearly 6,000 years ago.
- In 1913, Aldred Scott Warthin identified the genetic link to colon cancer.
- In 1932, Cuthbert Dukes described the stages of colon cancer and how the cancer develops.

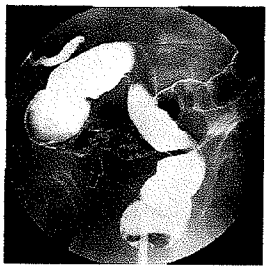


Clinical Features

- Familial adenomatous polyposis (FAP) caused by a mutation on the APC tumor suppressor gene (5q22.2) and shows autosomal dominant inheritance. Cause of 1% of all colon cancers.
- Lynch syndrome is caused by a mutation on MLH1 (3p22.2), MSH2 (2p21), MSH6 (2p16.3) or PMS2 (7p22.1). DNA reapair enzyme genes, and all show autosomal dominant inheritance. Causes 3- 5% of all colon cancers.

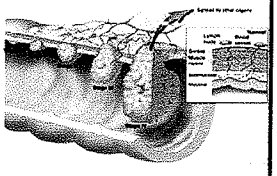
Diagnosing

- Genetic testing can be done if there is a family history of colon cancer.
- Colonoscopy- uses a scope to examine the inside of your colon and a biopsy can be taken and analyzed.
- Barium enema- A dye is placed in your colon and an X-ray is taken.
- Multiple CT scans- gives a virtual colonoscopy.



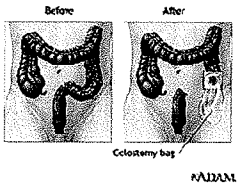
Stages

- 1: Cancer has grown through mucosa of the colon but has not spread beyond the colon.
- 2: Cancer has grown through the wall of the colon but has not spread to nearby lymph nodes.
- 3: Cancer has invaded nearby lymph nodes but not any other part of the body.
- 4: Cancer has spread to distant sites



Treatment and Disease Management

- Treatment depends on the stage of the cancer.
- Surgery can remove polyps in earlier stages or remove portions of the colon.
- Chemotherapy and radiation
- More than 1 million survivors.



Conclusion

- Colon cancer shows autosomal dominant inheritance.
- If diagnosed early, chances of survival are good, with over 1 million survivors.
- Gene defect does not always lead to cancer, it just increases the chance of developing cancer.

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- http://www.colonhealthadvice.com/who-discovered-colon-cancer.html

Multiple Choice Questions

1. Of the following, which is not a genetic syndrome that increases the risk of developing colon cancer?
   a. FAP
   b. Lynch Syndrome
   (c.) FGF
   d. HNPCC

Multiple Choice Questions

- What percentage of colon cancer is caused by a genetic defect?
  a. 1-3%
  (b.) 5-10%
  c. 3-5%
  d. 12-13%