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Acute Care
Pediatric Nurse Practitioner
Review Course 2020

Genetics

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MICHIGAN MEDICINE

Objectives

- Discuss general principles of genetic diseases
- Discuss common physical findings associated with genetic diseases
- Identify appropriate management and referral for common genetic problems affecting children

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BACKGROUND

Disorders of Amniotic Fluid Volume

High Risk pregnancies

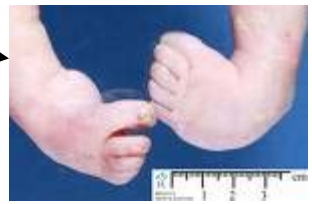
- Polyhydramnios
  - Excess amniotic fluid
  - > 2 liters in 3rd trimester
  - 1-3% of pregnancies
- Oligohydramnios
  - Too little amniotic fluid
  - < 500ml in 3rd trimester

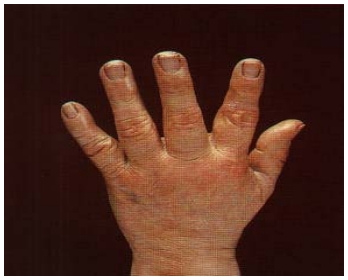
Polyhydramnios

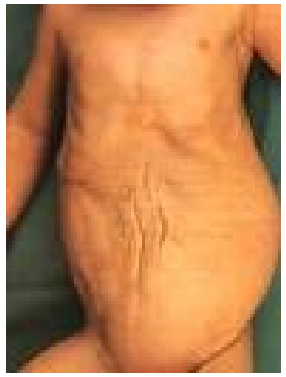
- Associated Conditions
  - Congenital Anomalies
    - Anacephaly
    - Hydrocephaly
    - Tracheoesophageal fistula
    - Duodenal atresia
    - Spinal bifida
    - Cleft lip/palate
    - Diaphragmatic hernia
  - Syndromes
    - Achondroplasia
    - Trisomy 18 and 21
    - TORCH
    - Hydrops fetalis

Oligohydramnios

- Intrauterine growth restriction (compression syndromes)
  - Clubfoot
  - Spadelike hands
  - Flattened nasal bridge
  - Large flattened ears
  - **Pulmonary hypoplasia**
- Twin-twin transfusion
- Renal agenesis
- Prune belly syndrome
- Chromosomal abnormalities
  - Trisomy 21, Tay-Sachs







SELECTED GENETIC DISORDERS

CHARGE Syndrome/Association

- Background
  - Described in 1979
  - Characteristic congenital features
  - Leading cause of deaf-blindness
- Etiology
  - 70% gene mutation in CDH7 gene; autosomal dominant

CHARGE Syndrome/Association

- Presentation
  - **C**: Coloboma of eye
  - **H**: Heart defects
  - **A:** Atresia of nasal choanae
  - **R**:Retardation of growth and/or development
  - **G**: Genital and/or urinary abnormlaities
  - **E**: Ear abnormalities/deafness
- Management
  - Treat each underlying condition (e.g. heart disease, choanal atresia)
  - May require hormone replacement for delayed puberty

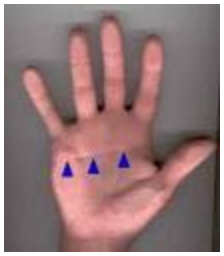
Trisomy 21 (Down Syndrome)

- Etiology
  - –Chromosomal anomaly – several kinds
  - –Non-disjunction trisomy 21: most common
- Incidence
  - –All races
  - –Both sexes affected equally
  - –Increased incidence with advancing maternal age
    - 25 year old mother 1:2000
    - 35 year mother 1:200
    - Over 40: 1:40 or higher

Trisomy 21

Clinical Examination Findings

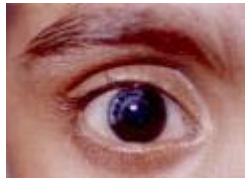
Extremities
- Short limbs
- Square hands
- Short, stubby fingers
- Short statue
- Simean crease



Head
- Flat occiput
- Short, thick neck
- Low set ears

Neck
- Webbed
- Risk for atlanto-axial instability
  - Increased mobility at 1st and 2nd cervical vertebrae
  - If excessive subluxation, may cause injury to spinal cord

Eyes
- Hypertelorism
- Upward, outward slant of palpebral fissure
- Whitish speckles (Brushfield spots)
- Strabismus
- Cataracts, later in life



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Trisomy 21

- Clinical Examination Findings
  - –Ears
    - Hearing loss
    - Recurrent serous otitis media
  - –Teeth malocclusion
  - –Heart
    - Congenital heart disease (up to 50% of patients)
      - – Atrial ventricular canal defect, most common
      - – Also Atrial septal defect and ventriculoseptal defect
  - –Gastrointestinal
      - – Duodenal or other atresias

Trisomy 21

- Genitals
  - Male: undescended testes; small penis; azospermia
  - Female: Large labia majora; small labia minora
- Hematologic
  - Incidence of leukemia 1:95 (~1%)
- Endocrine
  - Thyroid disease (15%)
- Neurologic
  - Hypotonia
  - Cognitive impairment; varying degree
  - Seizures

Trisomy 21

- Diagnosis
  - Prenatal
    - Amniocentesis, Chorionic villus sampling (CVS)
    - Percutaneous umbilical blood sampling
  - Postnatal
    - Karyotype/chromosomal studies
- Management
  - Interprofessional team management
  - Support breast feeding; may have poor tongue control
  - Monitor for sleep apnea
  - Monitor for ear infections/hearing loss; screen every 6 -12 months
  - Monitor thyroid function
  - Ophthalmology in first 6 months of life
  - Nutritional and behavioral guidance
  - Cervical radiographs for symptomatic children (neck or radicular pain, spasticity)

Refer to latest AAP guidelines for more information on screening and management

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Turner Syndrome

- Etiology
  - Exclusively affects girls
  - Karyotype, generally XO (80%); lack of one sex chromosome
- Incidence
  - 1:2500 live females
  - Accounts for approximately 10% of miscarriages

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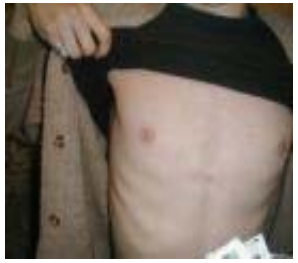
www.cafamily.org.uk

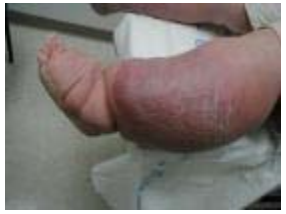
Turner Syndrome

- Clinical manifestations
  - WIDE spectrum of presentations
  - Overall
    - Short stature
    - Broad chest
    - Wide spaced nipples
  - Face/Neck
    - High palate
    - Under developed mandible
  - Neck, short webbed
  - Cardiac
    - Coarctation of aorta (70%), or other lesions



Turner Syndrome

- Kidney
  - Anomalies (60%); horseshoe kidney, duplicated collecting system
- Neurologic
  - Hearing loss, nystagmus, strabismus
- Infertility
  - Do not develop secondary sex characteristics
- Extremities
  - Lymphedema (30-40%); neonatal



Turner Syndrome

- Diagnosis
  - –Karyotype; sex chromatin study
- Management
  - –Surgical correction of heart lesion, if present
  - –Growth hormone; augment linear growth
  - –Estrogen replacement
  - –Ophthalmology evaluation
  - –Renal evaluation
- Outcomes
  - –Normal life span

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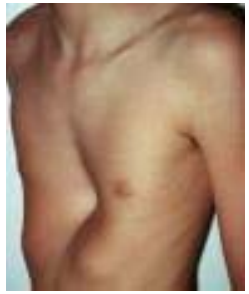
Fragile X Syndrome

- Etiology
  - Unusual mutational mechanism; 'dynamic' mutation
- Incidence
  - 1:2500 males; 1:2000 females
- Clinical manifestations
  - Head
    - Macrocephaly
    - Large ears
    - Prognathism (protruberant jaw)
    - High, arched palate
  - Eyes
    - Myopia
  - Cardiovascular
    - Mitral valve prolapse
    - Aortic dilation
    - Pectus excavatum



Fragile X Syndrome

- Neurologic
  - **Single most common form of inherited intellectual disability**
  - Cluttered speech
  - Autism
- Endocrine
  - Males: macroorchidism, tall stature
  - Females: ovarian cysts
- Extremities
  - Hyperflexible joints
  - Flat feet

Fragile X Syndrome

- Diagnosis
  - Molecular observation of expanded DNA segment of FMR1 gene
- Management
  - Medical management of seizures, if present
  - Early intervention with behavior therapy, education evaluation, and speech/occupational therapy support
- Normal life span

Trisomy 18 (Edwards)

- Background
  - –Chromosome disorder caused by additional chromosome 18
- Incidence
  - –1:3000 birth; 3:1 female predominance
- Clinical Manifestations
  - –Intrauterine
    - Intrauterine growth retardation
    - Decreased fetal activity
    - Frequently born post-term

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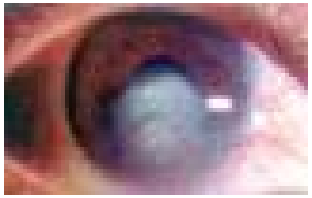
Trisomy 18 (Edwards)

- Overall
  - Failure to thrive
- Eyes/Ears/Mouth
  - Corneal opacity
  - Optic disc coloboma
  - Low set ears
  - Micrognathia
- Cardiac
  - Congenital heart disease
    - Ventricular septal defects
    - Valve abnormalities

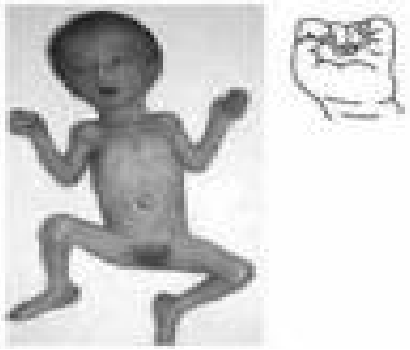


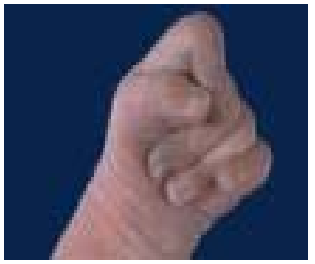
Trisomy 18 (Edwards)

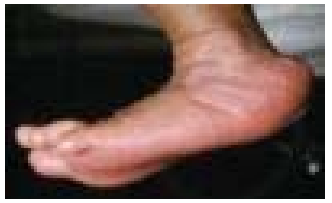
- Clinical Manifestations
  - Neurologic
    - Frequently, disturbance in cerebral or cerebellar development
    - Developmental delay
    - Generalized hypertonicity
    - Seizures
    - Meningomyeloceole
  - Gastrointestinal
    - Meckel's diverticulum
    - Esophageal atresia
  - Genitourinary
    - Cryptorchidism

Trisomy 18 (Edwards)

- Extremities
  - Tight flexion of fingers across palm
  - Index finger overlaps third digit
  - Occasionally, syndactaly
  - Inability to extend fingers
  - "Rocker bottom" feet
  - Radial malformation
  - May have transverse palmar crease
- Hematology
  - Congenital thrombocytopenia
- Other
  - Inguinal and umbilical hernias





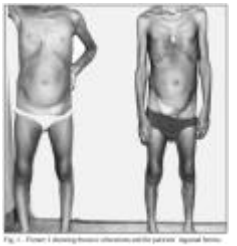


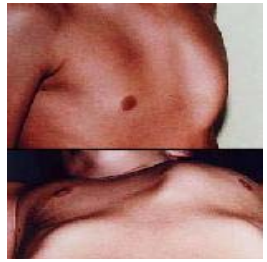
Trisomy 18 (Edwards)

- Management
  - –Symptom control
  - –Hospice/palliative care
- Outcomes
  - –50% die by one week of life
  - –Mean survival
    - Males: 58 days
    - Females: 282 days
  - –Profound intellectual disabilities in survivors

Marfan Syndrome

- Etiology
  - –Systemic disorder of connective tissue
- Epidemiology
  - –1 in 5 -10,000
  - –All ethnic groups
- Clinical Manifestations
  - –Skeletal
    - High degree of variability
    - Long limbs
    - Arm span > height
    - Joint hyper extensibility
    - Pectus carinatum or excavatum
    - Scoliosis
    - High, arched palate
    - Dental crowding





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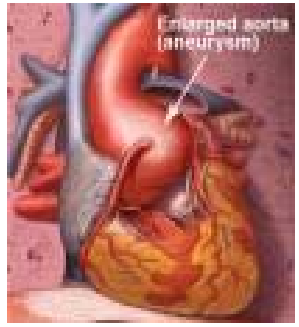
Marfan Syndrome

- Clinical Manifestations
  - –Cardiovascular
    - Aortic dilation
      - –*Risk of dissection!!*
    - Mitral valve prolapse
    - Dilation of main pulmonary artery
  - –Eye
    - Myopia; often severe
      - –Risk of retinal detachment
    - Lens subluxation
  - –Pulmonary
    - Spontaneous pneumothorax
    - Apical blebs
  - –Dura
    - Lumbosacral dural ectasia



www.mayoclinic.org

Marfan Syndrome

- Diagnosis
  - –Gene analysis
    - Mutation on chromosome 15
    - Not all deletions are detectable
    - **Diagnosis established on clinical evaluation
- Management
  - –Team of specialists
    - Geneticist, cardiologist, ophthalmologist, orthopedic surgeon
  - –Beta blocker therapy
    - –Decreases stress on aortic wall
  - –Exercise restriction
  - –Serial echocardiograms
    - –Replacement of aortic and mitral valves; repair of ascending aorta; when indicated

www.dinkopetkovic.hr

Inborn Errors of Metabolism (IEM)

- Definition
  - –Single gene defects
  - –Result in abnormalities in the synthesis or catabolism of proteins, carbohydrates or fats
  - –Effects result in:
    - Toxic accumulation of substrates before the block in pathway
    - Intermediates from alternative metabolic pathways
    - Defects in energy production and usage after the block
- Etiology
  - –Inherited gene defect

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Inborn Errors of Metabolism (IEM)

- Incidence
  - Rare individually
  - Of term infants that develop sepsis-like picture without known risk; 20% have IEM
  - Age and presentation VARY
  - Progression may be rapid and life threatening or slow and insidious
    - Depends on timing of significant accumulation of toxins
    - *Onset and severity may be exacerbated by diet, fasting or intercurrent illness*
  - Disorders of carbohydrate and protein metabolism and disorders of energy production typically present in newborn or early infancy
    - Generally rapidly progressing and severe
  - Disorders of fatty acid oxidation, glycogen storage and lysosomal storage disorders usually present in later infancy or childhood

Inborn Errors of Metabolism (IEM)

- *Any time infant/child presents with sepsis-like picture, hypoglycemia, mental status changes, IEM should be on the differential diagnosis*

Genetic Testing

- Increased availability
- Reasons for testing
  - Medical
  - Decision making
  - Family planning/recurrence risk
- Testing for:
  - Individual affected
  - At-risk family members
- Genetics consultation
  - Knowledge base/comfort level of PCP
  - Complex testing strategy
  - Need for detailed genetic counseling

Ethical/legal Considerations - Genetic Testing

- Incidental or secondary findings
  - –Unrelated to the condition for which the testing was ordered
  - – Variants of unclear clinical significance
  - – Discovery of false paternity or of consanguinity
    - Do not report unless safety of child is an issue

Question

When called to the emergency department to evaluate an otherwise healthy adolescent with a spontaneous pneumothorax, your differential diagnosis includes which of the following genetic conditions?

a. Turner syndrome

b. Marfan syndrome

c. Trisomy 21

d. CHARGE syndrome

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Answer:

When called to the emergency department to evaluate an otherwise healthy adolescent with a spontaneous pneumothorax, your differential diagnosis includes which of the following genetic conditions?

b. Marfan syndrome

Question

A child with hypoplastic left heart syndrome is being evaluated prior to heart transplant; which of the following karyotypes is most likely to be noted on genetic evaluation?

A. 46, XX
B. 45, X
C. 46, XY; 22 q 11 deletion
D. 47, XXY

Answer:

A child with hypoplastic left heart syndrome is being evaluated prior to heart transplant; which of the following karyotypes is most likely to be noted on genetic evaluation?

A. 46, XX

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Question

Which of the following statements is accurate about Fragile X syndrome? It is the most common cause of inherited:

a. Intellectual disability
b. Aortic root dilation
c. Infertility
d. Atlantoaxial instability

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Answer:

Which of the following statements is accurate about Fragile X syndrome? It is the most common cause of inherited:

a. Intellectual disability

Conclusions

- There are many genetic anomalies that affect children
- Within these genetic anomalies, there is often great variability
- Early recognition and treatment improves patient outcome

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