MEDICAL GENETICS AND CONGENITAL ANOMALIES

Rationale: Congenital anomalies play a major role in all of pediatric care. The leading cause of infant mortality in the United States is the sequelae of congenital anomalies. This exceeds the death rate for prematurity, SIDs, and other common causes of infant or neonatal death. Sixty percent of all admissions to a pediatric hospital are for conditions with a genetic basis. Three percent of all newborns have a recognizable congenital anomaly. An additional 2% of children have congenital anomalies that are not detectable in the newborn period. Finally, 3% of the United States population is mentally retarded, of which 80% is due to genetic factors. Primary care physicians involved in the provision of health care for children and adolescents need a basic understanding of how to evaluate and when to refer children with genetic disorders or other congenital anomalies.

Learning Objectives:
Upon completion of the clerkship the student will be able to:

1) Recognize the features of the more common pediatric genetic abnormalities (information may be found in Chapter 1 of Smith’s Recognizable Patterns of Human Malformations, 5th Edition):

- Trisomy 21 (Down Syndrome)
- Trisomy 18 (Edwards)
- Klinefelter Syndrome (XXY)
- Turner Syndrome (XO) 45,X
- Klinefelter Syndrome (XXY) 47,XYY
- Fetal Alcohol Syndrome
- Fragile X Syndrome
- Noonan Syndrome
- Prader-Willi Syndrome
- Rubinstein-Taybi Syndrome
- Angelman Syndrome
- Stickler Syndrome
- Marfan Syndrome
- Beckwith-Wiedemann Syndrome
- Russell-Silver Syndrome
- Osteogenesis Imperfecta
- VATER and CHARGE Association
- Pierre-Robin Sequence
- DiGeorge Syndrome
- Maternal PKU
- Maternal Diabetes, Infant of a Diabetic Mother (IDM)
- Fetal Exposure to Anti-convulsants
- Neurofibromatosis type I (von Recklinghausen type)
- Oculo-auriculo-vertebral Spectrum/Goldenhar Syndrome/Hemifacial Microsomia

2) Know unique medical and neurodevelopmental issues of the more common conditions listed above (bold).

3) Be able to categorize congenital anomalies as malformation, deformation, or disruption.

4) Understand the patterns of multiple congenital anomalies (syndrome, sequence anomaly, association).
5) Appreciate the psychosocial implications for families of children with congenital anomalies.

**Learning Activities:**

1. Lecture - 1 hour: Approach to the Patient with Congenital Anomalies

2. Patient Care Experiences: Genetics Outpatient Clinics

3. Independent Study
   A. Essential reading:

   B. Suggested References:

   C. Audio/visual:
      Several videotapes on children with multiple handicaps and clinical genetics are available for checkout through Meyer Rehabilitation Institute's Media Department (559-5745).

   D. Self assessment guide: to be available on UNMC Pediatric page of Intranet.

**Evaluation:** Final (summative) evaluation will be based upon clerkship performance and written examination.

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Approach to Congenital Anomalies and the Dysmorphic Child

I. INTRODUCTION - Incidence of Malformations and Genetic Disorders
   ____ Incidence of malformations at birth: 3%
   ____ By 5 years of age: 7-10% of children have evidence of a congenital structural anomaly.
   ____ Number of pediatric hospital admissions accounted for by genetic disorders: 5-10%
   ____ If conditions in which genetic factors are thought to play a role are included, some studies show that more than half of the pediatric hospital admissions are the result of genetic disorders.

II. COLLECTION OF DATA
   A. History
      1. Family history (pedigree)
         a. Pedigree symbols
         b. Pedigree examples (X-linked, autosomal dominant, autosomal recessive)
         c. Information obtained in the pedigree (other affected family members, consanguinity, infertility, spontaneous miscarriage, stillborns)
      2. Pregnancy history
         a. Parental age
         b. Fetal movement
            c. Teratogen exposure (drug, medications, chemicals, and other agents; maternal conditions; infections)
         d. Intrauterine growth
      3. Developmental history
      4. Medical history
   B. Morphologic Alterations
      1. Quantitative measurements (anthropometrics): height, weight, head circumference, inner canthal distance, outer canthal distance, interpupillary distance, palpebral fissure length, nasal-labial (philtrum) length, ear length, hand length, palm length, foot length, internipple distance, penile length, testicular volume, upper segment/lower segment ratio, arm span, ear rotation
      2. Qualitative/subjective observations
   C. Growth Pattern Analysis
      1. Prenatal (obstetricians’ reports, ultrasound, growth parameters at birth)
      2. Postnatal (relative size, proportionate growth, growth velocity)

III. LABORATORY AND IMAGING STUDIES
   A. Laboratory
      1. Karyotype
      2. Fluorescent in situ hybridization (FISH)
      3. Molecular (DNA) studies (linkage, direct)
      4. Biochemical
   B. Imaging
1. MRI
2. Skeletal survey
3. Bone age
4. Abdominal ultrasound
5. Echocardiogram
6. Other

IV. INTERPRETATION
A. Etiology vs. Pathogenesis
B. General Concepts
   1. Interpret in light of known embryology
   2. Timing
   3. Consider normal variation
   4. Consider familial variation
      5. Minor anomalies as clues (fontanelle size, dermal ridge patterns, hair patterns, mechanical forces, pathognomonic features, consistent features)
C. Pattern Recognition
   1. Single anomalies (malformation, deformation, disruption)
   2. Multiple anomalies (syndrome, association, sequence)

V. TREATMENT & COUNSELING
A. Treatment (if available)
B. Informative Counseling (prognosis and natural history, referral to other specialists, recurrence risk estimates, prenatal diagnostic studies, parental and patient support)
Teratogens

A. Fetal Alcohol Syndrome/Effect (FAS/FAE)
   1. Incidence 1.9 per 1,000 live births up to 1:300
   2. FAS features: Prenatal and postnatal growth deficiency, microcephaly, learning disabilities, developmental delay, psychosocial and behavior problems/ADHD and characteristic facial features. 20-50% with a documented exposure have other associated anomalies, including congenital heart disease.
   3. FAE features: In the absence of the physical stigmata and other congenital abnormalities of FAS, children with documented exposure who show characteristic neurobehavioral and psychosocial changes, including ADHD, impulsivity, learning disabilities, difficulty with abstract thinking.
   4. Treatment: Multidisciplinary with strong emphasis on consistent behavior management and coordination with the school, subsidized adoptions.

B. Maternal Diabetes, Infant of Diabetic Mother (IDM)
   1. 2 to 4 fold increase in major fetal malformations. Greatest risk in patient with poorest glycemic control during organogenesis.
   2. Features: Macrosomia, congenital anomalies, CHD, neural tube defects (NTD) including sacral agenesis, vertebral/skeletal anomalies, spontaneous Ab's, stillbirth, delayed lung maturity.

C. Maternal PKU
   1. Mothers with increased blood levels of phenylalanine (PHE) not on sufficient dietary treatment have up to 92% mental retardation, 72% microcephaly, 40% IUGR, 12% CHD. Lower incidence of defects with lower maternal PHE levels.
   2. Characteristic facies: Round, prominent glabella, epicanthal folds, midface hypoplasia, long, under developed philtrum.
   4. Incidence may be increasing as a generation of treated PKU girls reach child-bearing age.

D. Fetal Exposure to Anti-convulsants
   1. Important factors: fetal factors and dose, timing, duration, and combination of medications used. Some associations are fetal hydantoin with characteristic facies, growth and mental retardation, hirsutism, and nail hypoplasia. Neural tube defects with valproate. Also, congenital heart disease, growth retardation, developmental delays, CL/CP with various anticonvulsants.
   2. Maternal folate supplementation beginning three months prior to pregnancy.
   3. Prenatal genetic counseling.

E. Lithium
   1. Used to treat bi-polar depression
   2. Exposure during the first trimester presents an increase in risk for fetal heart malformations, particularly Ebstein’s anomaly. Alterations in cognition or behavior have not been noted in prenatally exposed children.
   3. Use around time of delivery may result in lithium toxicity in the neonate including neurological, cardiac, and hepatic dysfunction, goiter.
4. Secreted in breastmilk in significant amounts. High maternal doses may not be compatible with breast feeding; if lower doses are used and breastfeeding is attempted, the baby should be observed closely for side effects, and an infant serum lithium level (and perhaps thyroid evaluation) should be obtained periodically.

F. Cytomegalovirus
1. 0.2-2.2% of newborns have congenital CMV
2. About 10% of infants with congenital CMV infections exhibit serious clinical manifestations at birth (IUGR, microcephaly, CNS findings such as intraventricular calcifications, petechiae, hepatosplenomegaly, jaundice, and chorioretinitis).
3. 10-25% of children with congenital CMV (initially asymptomatic) develop abnormalities within the first few years of life including sensorineural hearing loss, chorioretinitis, neurological deficits, and dental defects.
4. Symptomatic manifestations are much less frequent in infants of women with recurrent infections.

G. Cocaine
1. Obstetrical complications such as pregnancy loss, IUGR, premature delivery, abruption.
2. Malformations, particularly those due to vascular disruption (intestinal atresia, gastroschisis, sirenomelia, limb reduction), have been infrequently reported following prenatal exposure. Anomalies of the genitourinary system, cardiac malformations, brain infarcts, and necrotizing enterocolitis have also been reported in exposed fetuses.
3. Maternal use in the third trimester has been associated with problems in the newborn period such as jitteriness, abnormalities in muscle tone, difficulty feeding, and impaired maternal-infant bonding.
4. Some studies have found long-term alterations in cognition (esp. speech) and behavior.
5. Cocaine is excreted in breastmilk in relatively large amounts, and cocaine toxicity has been reported in infants exposed via nursing.

H. There are numerous other medications, chemicals, physical agents, and infections that can harm the fetus or nursing infant. Nebraska has a Teratogen Information System that supplies current and comprehensive information to health care professionals (402-559-5071).