

## I. Types of Congenital Abnormalities

### a. Definitions:

- i. Morphological defects: abnormalities of structure visible at microscopic or higher levels
  1. Malformation: resulting from an intrinsically abnormal process
  2. Disruption: resulting from extrinsically induced breakdown on intrinsically normal process
- ii. Functional defects: physiological or behavioral deficiencies

## II. Congenital Abnormalities can arise from processes

### a. **Within the conceptus:**

- i. **Divergence:** one gene may affect many structures (**pleiotropy**) by participating in on or more cascades

#### 1. Within a gene:

- a. abnormality in a regulatory region can cause excess or deficiency of gene expression
  - i. Defective prechordal mesoderm may cause **Holoprosencephaly** (abnormal midline facial development) including hypotelorism (eyes close together), cyclopia (one eye), cleft lip and/or palate, microcephaly, brain defects in
  - ii. Mutation of sonic hedgehog can also cause holoprosencephaly
- b. abnormality in coding region can produce a defective protein that functions abnormally
  - i. **Kartagener syndrome:** dynein gene is abnormal, affects structures that involve motile cilia or flagella – situs inversus, respiratory tract defects, deafness, immotile sperm.
  - ii. Defective androgen receptors result in **Androgen Insensitivity Syndrome (Testicular Feminization Syndrome)**, where male develops externally as a female (failure to produce androgen would have the same effect)
- c. abnormal regulatory region activates expression of a normal protein at the wrong time or place
  - i. **Fragile X syndrome**
    1. results from a mutation in regulatory region of X chromosome gene
    2. physical and behavioral abnormalities and mental retardation

3. morphologically immature dendritic spines on many neurons
  4. defect in 5' untranslated region of the FMR1 gene on the X chromosome
2. Chromosomal abnormalities:
    - a. Deletion: Turner's Syndrome, 45 XO, is only whole chromosome deletion not fatal.
    - b. Excess: Klinefelter's, 47 XXY, and the trisomies of Down's 21, Edward's 18 and Patau's 13 (see M6 Table 8-1).
  3. At the cellular level (if one set of cells contributes to two or more structures)
- b. **Convergence:** many genes contribute to development of each structure; development is multifactorial
- i. Within Genes:
    1. Combinations of inputs can activate or inhibit a gene
    2. Hoxa-11 and Hoxd-11 genes in mice must both be deleted to effect development of radius and ulna.
  - ii. Within a Cascade:
    1. many defects can produce the same syndrome
      - a. ie feminization of genetic male
  - iii. Among the processes that generate an organ, organ system, or organism →
    1. cells have few behaviors (secrete, move, divide, die)
    2. structures absent, reduced, incomplete, or excessive
    3. include renal agenesis, anophthalmia, microphthalmia, microcephaly, congenital diaphragmatic hernia, cleft lip or palate, omphalocele, polydactyly
  - iv. at the organ system and organism level
    1. growth retardation
    2. neurological abnormalities
    3. increased incidence of spontaneous abortion, premature delivery, infant mortality

### III. Within the parents

- a. Maternal conditions that can make a genetically normal conceptus develop abnormally
  - i. Mechanical deformation
    1. oligohydramnios
    2. amniotic bands
    3. constraint by maternal pelvis (very thin women may have growth-restricted fetus)
    4. A genetically normal but mechanically deformed fetus may develop a normal shape after birth
  - ii. Maternal Endocrine

1. hypothyroidism
  2. adrenal tumor → excess androgens
  3. maternal diabetes → excessive growth (heart, spleen, liver, umbilical chord, body fact, respiratory distress syndrome)
- iii. Maternal Obesity
1. ↑ risk of infertility
  2. ↑ risk of maternal pathophysiology
  3. ↑ risk of birth defects
  4. contributes to premature birth
  5. ↑ likelihood of Caesarian section

#### IV. Environment and Parental Behavior

- a. Important Considerations
  - i. Placenta is not a barrier to most teratogens
  - ii. Determining teratogens and their mechanisms of action is difficult
  - iii. Teratogens can alter germ cells of an embryo and affect future generations
- b. Classes of Teratogen
  - i. Infectious agents
    1. e.g. Rubella virus: cataract, cardiac malformation, deafness
  - ii. Radiation
    1. e.g. X-rays
  - iii. Chemicals
    1. Deficiencies of normal chemicals
    2. Pollutants, medications, recreational drugs
- c. Response to teratogen is **multifactorial**:
  - i. dose of teratogen
  - ii. critical periods of development
    1. Each teratogen has a period of maximum risk for exposure
    2. During first two weeks after fertilization (before gastrulation and organogenesis), teratogen may produce extensive damage (fetus dies)
    3. Most organ-critical period is weeks 4 through 9 (during organogenesis)
    4. For CNS, most critical period begins in week 3 and lasts through 4<sup>th</sup> month
    5. Systems with prolonged sensitivity continue developing after birth: nervous system, eyes, external genitalia, the skeleton and teeth
  - iii. genotype (genetic constitution) of embryo
  - iv. family history
    1. familial tendencies, individual variation, social factors
- d. **Fetal alcohol damage**
  - i. Both parents

- ii. Minimal estimate 3/1000 live births. May be most common cause of mental retardation in US
  - iii. Holoprosencephaly or abnormal facial features, growth retardation, abnormal nervous system
  - iv. 1<sup>st</sup> trimester: facial malformations; 2<sup>nd</sup> trimester: decreased neurogenesis; 3<sup>rd</sup> trimester: death of existing neurons, interferences with nervous system development
  - e. **TORCH**: acronym for Toxoplasma gondii, other (syphilis, varicella), rubella, cytomegalovirus, herpes simplex virus are infectious agents that cross placenta.
  - f. **Cigarette smoking**: Nicotine constricts uterine blood vessels, causing decrease in uterine blood flow.
  - g. **Cocaine**: retarded growth, stiff limbs, higher risk of crib death, learning deficits.
- V. How can physicians deal with Congenital Abnormalities?
- a. Treatment
  - b. Prevention
    - i. Know the effect of medications
    - ii. Treat pre-existing conditions
    - iii. Encourage family planning
    - iv. Provide equivalent info to all parents
  - c. Encourage research to assess environmental risks