Dysmorphic Features:
Common Syndromes and Sequences

Background

1. Dysmorphic features:
    - Abnormal body variations that can be measured or characterized (congenital anomalies or "birth defects")
        - Singular anomalies often diagnostically insignificant
        - Multiples anomalies can aid in diagnosis of a larger syndromes
2. Epidemiology of dysmorphology
    - Incidence of major malformations is approximately 2-3% of live births
    - Congenital malformations account for approximately 20% of infant deaths
3. This summary is limited to common congenital sequences and syndromes

Pathophysiology

1. Etiology is diverse but may include genetic, infectious, chemical or metabolic causes
    - Physical causes may include decreased amniotic fluid, compression, torsion
2. Different organ systems are susceptible to teratogenesis during different stages of development
    - Most major malformations occur in the embryonic period (3 to 8 wks)
    - Functional defects and minor malformations may occur throughout the fetal period (9-38 wks)
        - CNS, sensory organs, teeth, and external genitalia remain susceptible

Common Congenital Sequences and Syndrome

1. Autosomal syndromes
    - General patterns
        - Frequency of chromosomal disorders increases with maternal age
        - Frequency of recurrence depends on whether the cause is a chromosomal translocation (higher recurrence risk, independent of maternal age)
    - Trisomy 21
        - M/c pattern of malformation (approximately 1 in 660 infants)
        - Most cases are full trisomy 21; a minority (approximately 5%) are either mosaic or translocation
        - Clinical findings
            - Mental deficiency
            - Hypotonia, hyperflexibility of joints, flat facial profile, protruding tongue, loose nuchal skin
            - White specks on iris (Brushfield spots)
            - Single transverse palmar crease
            - Pelvic dysplasia
            - Wide gap between first and second toes ("sandal gap")
        - Associated with cardiac defects (approx 40% of cases), immune dysfunction, lymphoma, atlantoaxial dislocation

        - Resources for patients and families available at http://www.ndss.org/
    - Trisomy 18
        - Approximately 3 in 1000 newborns
            - Ratio 3:1 female:male
        - Almost all cases are full trisomy without translocation; therefore recurrence risk is low (less than 1%)
        - Clinical findings
            - Severe mental deficiency
            - Feeble activity, weak cry, micrognathia
            - With clenched fist, overlapping of index finger over third, fifth finger over fourth
            - Hypoplasia of nails
            - Mild hirsutism of forehead and back
        - Associated with cardiac defects, horseshoe kidney, cleft lip / palate, and many other defects; median survival time is 14.5 days
            - Rarely, may survive into childhood (particularly with mosaic or partial trisomy)
        - Resources for families available at http://www.trisomy18.org/
    - Trisomy 13
        - Approximately 1 in 5000 births
        - Clinical findings
            - Severe mental deficiency; holoprosencephaly
            - Microcephaly, micropthalmia, cleft lip / palate, abnormal auricular helices
            - Polydactyly, narrow fingernails, single transverse palmar crease
            - Cryptorchidism, abnormal scrotum in males
        - Associated with cardiac defects, deafness, polycystic kidney; median survival time is 7 days
        - Resources for families available at http://www.livingwithtrisomy13.org/
2. Sex chromosomal syndromes
    - XXY syndrome (Klinefelter syndrome)
        - Approximately 1 in 660 males
            - Usually diagnosed in adolescence or young adulthood
            - Diagnosis in childhood is helpful in allowing for testosterone replacement
        - Clinical findings
            - Mild mental deficiency (mean IQ between 85 and 90); deficiency particularly in expressive language, processing, and auditory memory
            - Long limbs, slim stature
            - Hypogonadism, hypogenitalism
        - May be associated with severe acne, cryptorchidism, scoliosis, diabetes mellitus (in adulthood), breast cancer, osteoporosis, autoimmune disease
        - Resources for patients and families available at http://klinefeltersyndrome.org/

- 45X syndrome (XO syndrome, Turner syndrome)
  - Approximately 1 in 2500 newborn females
    - Most 45X conceptuses die before birth
  - Clinical findings
    - Mild mental deficiency (mean IQ 90)
    - Small stature
    - Prominent ears, webbed posterior neck, low hairline
    - Broad chest ("shield chest")
  - Associated with horseshoe kidney, cardiac defects, ovarian dysgnesis ("streak ovaries")
  - Resources for patients and families available at http://www.turnersyndrome.org/

3. Genetic syndromes
   - Fragile X syndrome
     - Approximately 1 in 5000 males; rarer in females
       - Generally familial (high rate of recurrence)
     - Clinical findings
       - Mild to profound mental deficiency
       - Macrocephaly, long facies, large ears, epicanthal folds
       - Macrorchidism (post-puberty)
     - Associated with hyperkinetic behavior, emotional instability, autistic features; abnormalities exist on a continuum depending on the number of repeats
     - Resources for patients and families available at http://www.fragilex.org/
   - Marfan syndrome
     - Autosomal dominant inheritance
     - Clinical findings
       - Normal intelligence, but may show learning disability or attention deficit disorder
       - Tall stature; long slim limbs; muscular hypotonia
       - Pectus carinatum
       - Wrist and thumb sign
       - Lens subluxation; defect in suspensory ligament
     - Associated with cardiac defects (esp. dilation of ascending aorta), retinal detachment, diaphragmatic hernia
     - Resources for patients and families available at http://www.marfan.org/
   - Treacher-Collins
     - Autosomal dominant inheritance
     - Clinical findings
       - Malar hypoplasia
       - Slanting palpebral fissures
       - Mandibular hypoplasia
       - Malformation of auricles; external ear canal defect; conductive hearing loss

        - Intelligence is normal
            - Therefore early recognition of deafness is important
            - In order to provide hearing aids or surgery for proper development
        - Plastic surgery in childhood may also offer cosmetic improvement
        - Resources for patients and families available at http://www.treachercollins.org
4. Teratogenic syndromes
    - Fetal alcohol syndrome
        - Due to exposure of the fetus to alcohol during pregnancy
        - Clinical findings
            - Mental retardation (moderate to profound) and brain malformations (e.g. agenesis of corpus callosum)
            - Smooth philtrum
            - Maxillary hypoplasia
            - Microcephaly
            - Short palpepbral fissures
            - Nail hypoplasia
        - Note that there is no "safe" stage during pregnancy to consume alcohol
        - Resources for patients and families available at http://www.nofas.org/

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