

## Management of Children With Common Syndromes and Birth Defects

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- I. Principles and premises:
  - A. Prevention and early intervention are beneficial
  - B. The benefits are greatest when interventions are applied to those at highest risk
  - C. Identifying individuals who are at increased risk depends on accurate diagnosis
  
- II. **Down syndrome**
  - A. Incidence: 1/750 live births  
65-80% are spontaneously aborted, = 1/200 conceptions
  
  - B. Genetics:

Trisomy 21	95%	
Translocations	2-3% (~30% inherited)	
Mosaic	2-3%	

  

Maternal age risk	30	1/420	
(DS only)	35	1/360	(Most are born to young mothers)
	40	1/100	
	45	1/30	
  
  - Prenatal screening: Serum alpha fetoprotein  
"Triple Screen"
  
  - Empiric recurrence risk for trisomy 21 = 1%. Risk to father who is a balanced translocation carrier = 4%, mother = 10%
  
  - C. Major features
    1. Mental retardation of varying severity; the severity is not predictable in infancy
    2. Short stature (Use Down syndrome growth charts!)
    3. Low muscle tone
    4. Dysmorphism
      - flat occiput and midface
      - small upslanting eyes
      - Brushfield spots of the iris
      - small "squared" ears
      - small nose
      - protruding tongue

excess skin at the base of the neck  
 bell shaped chest  
 short upper arms and thighs  
 short fingers  
 incurved 5th finger (clinodactyly)  
 single palmar crease (45%)  
 sandal gap between 1st and 2nd toes

5. Diagnostic features in the newborn:
- |                          |     |
|--------------------------|-----|
| flat facial profile      | 90% |
| poor Moro reflex         | 85% |
| hypotonia                | 80% |
| joint hyperextensibility | 80% |
| excess neck skin (nape)  | 80% |
| upslanting eyes          | 80% |
| ear abnormalities        | 60% |
| incurved 5th finger      | 60% |
| single palmar crease     | 45% |

D. Medical complications

1. Congenital heart defects - 30-50%
 

AV canal	1/3
VSD	1/3
Other	1/3
- Acquired aortic root dilatation and aortic valve insufficiency
2. GI: TE fistula, pyloric stenosis, duodenal atresia, annular pancreas, Hirschprung's, imperforate anus
3. Auditory and visual impairments
4. Hypothyroidism - 40% lifetime risk
5. Obstructive sleep apnea
6. Excessive upper respiratory and ear infections
7. Hematologic abnormalities (any cell line), including leukemia
8. Atlanto-axial instability (15%)
9. Alzheimer disease
10. Immunologic dysfunction: recurrent infections (true immunodeficiency is rare), autoantibodies, accelerated aging

E. Life expectancy to age:

	<u>with CHD</u>	<u>w/o CHD</u>
1	76%	91%
5	62%	87%
10	57%	85%
20	53%	82%
30	50%	80%
50	60%	
60	40%	
68	14%	

- F. Monitoring: echocardiogram in infancy  
annual neuro exam, T4, TSH; awareness of leukemia signs/sx  
cervical spine films (flexion/extension) at age 2,  
and 10 or 11  
audiology, ophthalmology at age 1  
sleep study? (low threshold)

### III. **Turner syndrome**

- A. Incidence: 1/2500 live births; 98% are spontaneously aborted (20% of all sa's)
- B. Genetics: 45,X (50%); mosaic (45,X/46,XX or 45,X/46,XY;others) = 35%
- C. Major features: (often mild)
1. Lymphatic obstruction in embryonic life (~1/5, most 45,X):  
fetal hydrops  
cystic hygroma --> webbed neck  
congenital edema  
deep nail beds
  2. Short stature @ 5-10 years (~1/3, but increasing) - ?due to blunted response to growth hormone
  3. Gonadal dysgenesis (~1/3, but decreasing):  
infertility (99%)  
Primary amenorrhea (90%); secondary in 5-10%  
lack of breast development at puberty
- D. Associated problems:
1. Heart defects(20-45%):coarctation (15%), VSD, ASD, bicuspid AV, other (MVP, Hypoplastic LV, HTN, conduction defects)
  2. Renal/urinary tract anomalies (30-70%): Horseshoe kidney, ectopic kidney, duplications of the collecting system
  3. Lymphedema - usually resolves in childhood
  4. Recurrent otitis, small ear canals
  5. Gonadoblastoma in 45,X/46,XY mosaicism
  6. Endocrine: Hypothyroidism (~20%), <1/2 in childhood – most in 20's - 30's  
Diabetes/glucose intolerance
  7. Normal intelligence, but increased incidence of learning disabilities related to visual-spatial defects. MR if ring chromosome...
  8. Predisposition to form keloids
  9. Predisposition to obesity

- E. Management:
1. Close attention to cardiovascular status (examine at 1 week)
  2. renal ultrasound
  3. Periodic T4, TSH, fasting blood sugar?
  4. If 45,X/46,XY mosaic, prophylactic gonadectomy is indicated
  5. Be wary of cosmetic surgery
  6. Supraphysiologic doses of growth hormone

IV. ***Klinefelter syndrome***

- A. Incidence: 1/600 - 1/1000
- B. Genetics: 47,XXY (80%), mosaic (10%), other, eg XXXY (10%).  
Nondisjunction; weak maternal age effect.
- C. Diagnosis: Incidental (esp. prenatal), clinical at puberty, infertility.  
Many are likely not identified.
- D. Features: mild tall stature, normal lifespan and mortality  
hypogonadism: small testes after puberty  
normal phallus  
gynecomastia (= risk of breast cancer)  
infertility (99%)  
some have female body habitus and body hair distribution  
average verbal IQ = 90, performance IQ 100 (most have normal intelligence)  
some learning disability, speech delay, sensory integration problems,  
behavior problems in adolescents and adults;  
aggressiveness, depression, "antisocial" behavior;  
shy, immature, nonassertive
- E. Testosterone therapy may help with body image issues and behavior problems

V. ***XXY***

- A. Incidence: 1/1000
- B. Features: variable tall stature  
some learning disability, speech delay, sensorimotor integration  
slightly higher incidence of mental retardation, but most have normal intelligence  
slightly higher incidence of antisocial/criminal behavior, but most men with this behave normally

## VI. *Marfan syndrome*

- A. Incidence: 1/10,000
- B. Genetics: Autosomal dominant  
New mutations are common (30% of cases)  
Paternal age effect
- C. Features: (\*\* = specific to Marfan syndrome)
  - 1. Skeletal: tall stature
    - \*\* skeletal disproportion: low U/L segment ratio
    - arm span > 1.05 x height
    - long hands and feet for height
    - long fingers for hand length
    - joint hypermobility
    - scoliosis
    - pectus excavatum or carinatum
  - 2. Ocular:
    - myopia
    - \*\* upward dislocation of the lenses (50-80%)
  - 3. Cardiovascular: mitral valve prolapse
    - \*\* aortic root dilatation/dissection
  - 4. Other: high/narrow palate  
spontaneous pneumothorax

- D. Diagnostic criteria:  
For an index case: major criteria in at least 2 organ systems and involvement of a third, *or* presence of a mutation known to cause Marfan syndrome, one major criterion in an organ system, and involvement of another.

For a relative of an affected individual:

A first degree relative (parent, sib, child) who meets the criteria for an index case, plus one major criterion in an organ system and involvement of another

Organ systems:

- 1. Skeletal - Major criterion = presence of 4 of: pectus carinatum, pectus excavatum requiring surgery, reduced upper to lower segment ratio or arm span to height ratio >1.05, wrist and thumb signs, scoliosis >20 degrees or spondylolisthesis, reduced elbow extension (<170 degrees), pes planus due to medial displacement of the medial malleolus, protrusio acetabulae (by x-ray).

Minor criteria = pectus excavatum not requiring surgery, joint hypermobility, high arched palate with dental crowding, facial features.

Involved = at least 2 components of the major criterion, or one of those plus 2 minor criteria.

2. Ocular - Major criterion = ectopia lentis

Minor criteria = abnormally flat cornea by keratometry, increased axial length of the globe by ultrasound, hypoplastic iris or ciliary muscle causing impaired pupillary constriction (miosis) and dilatation (mydriasis) as well as fluttering with eye movement (iridodonesis).

Involved = presence of at least 2 minor criteria

3. Cardiovascular -

Major criteria = dilating ascending aorta involving at least the sinuses of valsalva, or aortic dissection

Minor criteria = mitral valve prolapse, main pulm artery dilatation not due to PS below the age of 40, calcification of the mitral valve annulus before the age of 40, dilatation or dissection of the descending aorta below age 50.

Involvement = a major criterion or one minor criterion

4. Pulmonary - Major criteria = none

Minor criteria = spontaneous pneumothorax or apical blebs by x-ray

Involved = one minor criterion

5. Skin - Major criteria = none

Minor criteria = striae not due to marked weight changes, pregnancy, or repetitive stress; recurrent or incisional hernias

6. Dura - Major criterion = dural ectasia by CT or MRI

Minor criteria - none

7. Family/genetic history -

Major criterion = parent, child, or sib who meets the diagnostic criteria independently; presence of an FBN1 mutation known to cause Marfan syndrome; presence of a haplotype known to be associated with Marfan syndrome in the family

E. Management: yearly echocardiogram and eye exam  
prophylactic atenolol

avoidance of contact sports (including soccer and basketball) and isometric exercise and other strenuous activities which involve the Valsalva maneuver (swimming, bicycling are some good alternatives)

## VII. *Neurofibromatosis*

- A. Incidence: 1/4000
- B. Genetics: Autosomal dominant  
New mutations are common (40-50%)  
Highly variable severity
- C. Diagnostic criteria (need 2):
  1. 6 or more cafe au lait macules at least 5mm in size in children, 15mm in post pubertal adolescents and adults
  2. 2 or more simple neurofibromas, or one plexiform neurofibroma
  3. axillary or inguinal freckling
  4. optic glioma
  5. 2 or more Lisch nodules
  6. distinctive osseous lesion such as pseudarthrosis of the tibia or sphenoid wing hypoplasia
  7. a first degree relative who meets 2 of the preceding criteria
- D. Complications: Affect a minority of patients, probably 5-10%
  1. Central nervous system tumors
  2. other malignancies: neurofibrosarcoma, ?leukemia, ?Wilm's tumor
  3. Hypertension, sometimes due to pheochromocytoma or renal artery impingement by a neurofibroma in the vessel wall
  4. learning disabilities and cognitive impairment
- E. Management:
  1. Frequent blood pressure measurement, yearly at a minimum. If elevated, ultrasound of the renal artery and urinary catecholamines are indicated.
  2. Annual neurological exams looking for evidence of mass lesions; neuroimaging only if abnormalities are detected on exam.
  3. Early intervention programming as needed
  4. Annual ophthalmologic exams in childhood to look for signs of optic glioma.

## APPROACH TO CHILDREN WITH CONGENITAL ANOMALIES

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### Objectives:

1. List 2 ways in which early identification of congenital anomalies and establishing an underlying diagnosis can be beneficial to patients and their families.
2. Identify historical and physical clues to the significance of congenital anomalies.
3. Obtain additional historical, physical, and laboratory data appropriate for the further evaluation of a patient with congenital anomalies.
4. Define and apply terms commonly used in the description of congenital anomalies.

### Background:

Incidence: Major anomalies (those requiring surgery or ongoing medical care) affect 3-7% of all live born infants, depending on the age at detection:

Newborns	3%
1 year	5%
5 years	7%

Minor anomalies: 15% of newborns have 1; 1% have 3 or more; 90% of those with 3 or more have a major anomaly as well.

Impact: second only to complications of prematurity (and may soon exceed them) as the leading cause of death in the first month of life, and second only to accidents between 1 and 5 years. It is estimated that more than 15 million Americans are disabled as the result of congenital anomalies.

Etiologies:	Chromosome rearrangements	5-10%
	Single gene defects	10-15%
	Environmental (nongenetic) factors	10%
	Polygenic/multifactorial causes	35-40%
	Unknown	30%

- I. *Why seek a diagnosis for suspected congenital anomalies?*
  - A. Facilitates optimal medical and surgical care when the natural history of the disorder is well understood:  
  
examples: Down syndrome  
Turner syndrome  
Beckwith-Wiedemann syndrome  
Midline vs. Bilateral cleft lip and palate  
Multiple congenital contractures

B. Counseling issues:

1. Acceptance of the child and any attendant disabilities.
2. "Why did this happen?" - an obstacle to coping
3. "Will it happen again?" - recurrence risk estimation

II. *When should I be suspicious that congenital anomalies might be significant?*

A. Prenatal history

1. abnormal fundal height progression
2. abnormal fetal movement: onset >20 weeks  
character ("swimming")  
diminished activity  
position at birth
3. prenatal exposures: drugs  
infections (TORCH)  
maternal illness (diabetes, epilepsy)
4. abnormal prenatal screening tests:  
alphafetoprotein (AFP)  
"triple" screen
5. ultrasound: high or low amniotic fluid volume  
visible anomalies  
fetal growth abnormalities

B. Postnatal history

1. Asphyxia
2. Feeding problems
3. Neurological abnormalities (seizures, lethargy, hypotonia, hypertonia)
4. Biochemical abnormalities (hypoglycemia, hypocalcemia, acidosis)
5. Abnormal growth, especially proportionate (wt = length = OFC) growth failure, overgrowth, asymmetry, skeletal disproportion
6. Presence of other anomalies
7. Developmental delay/mental retardation

C. Family history

1. congenital anomalies
2. mental retardation
3. recurrent pregnancy losses
4. unexplained neonatal death(s)
5. parental ages
6. consanguinity

III. *How are morphological features analyzed and described?*

- A. Gestalt ("Walk in the room" impression)
- B. Detailed exam with measurements
- C. In addition to the above, interpreting significance of findings must take into account;
  - 1. what's normal for the family
  - 2. embryologic and developmental processes
  - 3. changes in the phenotype over time
- D. Photographs
- E. Laboratory studies

1. Chromosome analysis

Indications: Major anomalies of 2 or more organ systems or 1 major anomaly and 2 minor anomalies, growth impairment or developmental delay/mental retardation

2. Biochemical testing:

Indications: Metabolic acidosis, lethargy, vomiting, seizures, jaundice, E.coli sepsis, abnormal odor, loss of developmental milestones

3. Radiographs

Indications: Positional abnormalities, torticollis, abnormal skull shape, disproportionate or asymmetric growth, limb deficiencies

4. DNA studies (limited)

IV. When is a Genetics evaluation indicated for infants with congenital anomalies?

- A. For diagnosis
  - 1. Any infant with more than one major anomaly, or one major and multiple minor anomalies.
  - 2. Any infant with one or more major anomaly and/or multiple minor anomalies, and a family history of congenital anomalies, recurrent pregnancy losses (>2), neonatal death, mental retardation, or parental consanguinity.
  - 3. Any infant with anomalies and a history of exposure to a potential teratogen during the pregnancy.

- B. For management of an established diagnosis
  1. Recommendations for expectant management of associated complications
  2. Coordination of tertiary care
  3. "Parallel" care (e.g., skeletal dysplasias)
  
- C. For counseling
  1. Grief
  2. Recurrence risks
  3. Identification of resources for additional support

V. *Terminology*

- A. For constellations of anomalies
  1. Syndrome: Pathologically related anomalies which occur together more often than expected by chance (e.g. Down syndrome).
  2. Sequence: a constellation of anomalies derived from one primary anomaly (e.g., Robin sequence).
  3. Developmental field defect: anomalies resulting from disturbed development of a related group of cells in the embryo (e.g., midline anomalies)
  4. Association: anomalies that occur together more often than expected by chance but whose pathogenetic relationship is unknown (e.g., VACTERL, CHARGE).
  
- B. For pathogenetic processes
  1. Malformation: Defect caused by intrinsically abnormal morphological development (e.g., neural tube defects, cleft lip & palate)
  2. Deformation: Defect of structure or position resulting from the action of abnormal extrinsic mechanical forces on intrinsically normal development (e.g., club foot from intrauterine compression).
  3. Disruption: Defect caused by extrinsic breakdown of or interference with originally normal development (e.g., amniotic bands).

4. Dysplasia: Abnormal organization of cells and tissues (e.g., skeletal, connective tissue dysplasias).

C. Other

1. Anomaly: any abnormal characteristic
2. Dymorphic: abnormally formed
3. Congenital: present at birth (not necessarily genetic)
4. Genetic: caused by the action of one or more genes
5. Familial: occurrences within a family (not necessarily genetic)

VI. *Syndromes rarely identified in the newborn period:*

- A. Klinefelter (47,XXY)
- B. Many cases of Turner syndrome incidentally diagnosed
- C. Williams syndrome
- D. Most cases of Noonan syndrome
- E. Fragile X syndrome unless there is a positive family history
- F. Storage diseases

**Counseling parents of children with congenital anomalies:**

1. If anomalies are identified during the pregnancy, the information at hand is often insufficient or ambiguous. Parents must be helped through the processes of adjusting to the loss of the baby they thought they would have, and coming to terms with the prospect of having a child with birth defects. The physician's role is to make sure the parents understand what is and is not known about the identified anomalies, their prognostic implications, and options for further evaluation and management. This must be done in an open, supportive, and compassionate manner.
2. Anomalies identified at birth also require early (in the delivery room), open, and compassionate discussion with the family, and an urgent diagnostic evaluation.
3. Guilt, shock, anger, sadness, and helplessness are all normal and expected reactions to this news, though different individuals will experience them at different times. It is not appropriate to attempt to protect parents from these feelings except in extreme and extraordinary circumstances.