

## 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 | (Most are born to young mothers) |
| (DS only)         | 35 | 1/360 |                                  |
|                   | 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
2. Acquired aortic root dilatation and aortic valve insufficiency
3. GI : TE fistula, pyloric stenosis, duodenal atresia, annular pancreas, Hirschprung's, imperforate anus
4. Auditory and visual impairments
5. Hypothyroidism - 40% lifetime risk
6. Obstructive sleep apnea
7. Excessive upper respiratory and ear infections
8. Hematologic abnormalities (any cell line), including leukemia
9. Atlanto-axial instability (15%)
10. Alzheimer disease
11. 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. ***XYY***

- 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.