The Top 10 Dysmorphic Syndromes: Keys to Diagnosis/What’s Hot

Kenneth N. Rosenbaum, MD
Children’s National Health System
Washington, DC
Conflict of Interest Disclosure

Dr. Rosenbaum has no financial interests, arrangements, affiliations, or any bias with any of the corporate organizations offering financial support or educational grants for this program.
Top 10 Dysmorphic Syndromes

• Keys to diagnosis/important clues
  – Expect variability in presentation
  – Be aware of heterogeneity
  – Low threshold for diagnosis

• Management of expected issues

• New advances/what’s hot
Down Syndrome

• Incidence 1/650 births; 1/270 mid-trimester
• Diagnosis based on number of minor variations; use available systems (Hall)
• Important to be comfortable with clinical diagnosis prior to cytogenetics
Down Syndrome-Management

• Chromosomes (rapid FISH)
• ECHO
• CBC, thyroid function
• Auditory screening
• Specialty involvement
• Intervention referral, support groups
• AAP Health Supervision for Children with Down Syndrome, 2011
Down Syndrome-Advances

• Rapid diagnosis
• Improved outcomes?
• Pharmaceutical trials?
• Silent issues (thyroid, celiac, OSA)
• Significant risk for dyspraxia, attention deficit, autistic spectrum disorder
Down Syndrome-Advances

• Maryland Senate bill 654: authorizing provision of information
• Non-invasive prenatal testing
  – Maternal cell-free DNA; 1st trimester
  – Aneuploidy screen
  – ~99% detection rate for Down syndrome
• Digital remote diagnosis
Digital Dysmorphology

1 Principal Mode

Down syndrome  Healthy group

Down syndrome  Healthy group

Automatic Facial Analysis and Diagnosis from Photography.
Creation of Knowledge

- Photography analysis for **genetic screening**
- Simple, non-invasive, accurate, **affordable and instant**
- Remote **diagnosis (97% accuracy)** – as dysmorphologists
- Various syndromes
Sex Chromosome Abnormalities

- Common, share similar frequency (1/1000)
- 47,XXY;47,XYY;47,XXX
- Prenatal diagnosis group large proportion
- Not dysmorphic
- Normal, but slightly decreased cognition
- Expressive language delay fairly universal
Sex Chromosomes-Advances

• Klinefelter syndrome
  – Early testosterone loading?
  – At-risk for academic difficulties
  – Increased risk for breast cancer
  – Risk for offspring with sex chromosome aneuploidy
Turner Syndrome

• Incidence 1/2500 females
• High fetal lethality (~99% of conceptuses)
• Highly variable phenotype (1/3 nursery, 1/3 childhood, 1/3 adolescent)

• Diagnostic keys
  – Edema
  – Cardiac (BAV, coarctation)

• Normal cognition
• Abstract math reasoning
Turner Syndrome - Management

• Chromosomes (rapid FISH)
• Evaluation for additional malformations
  – ECHO, renal sono
• Thyroid function
• Specialty consultation
Turner Syndrome-Advances

- Increased risk for auto-immune disorders (thyroid, diabetes, GI)
- Later-onset risk for aortic dilatation
- Growth hormone supplementation
  - Timing?
- Fertility
  - Assisted reproductive technologies
Fragile X Syndrome

- Most common inherited cause of intellectual disability (1/2500 males, 1/5000 females)
- Secondary to expansion of CGG repeats
  - Full mutation >200; premutation 55-200
- Females more mildly affected
- Long face, prominent forehead & ears, large testes
- Behavioral phenotype (gaze aversion)
Fragile X Syndrome-Advances

- Awareness of gray zone alleles (45-54)
- Refinement of risk for expansion/AGG interruptions
- Risks for premutation carriers
  - Premature ovarian failure
  - Fragile X tremor ataxia syndrome (FXTAS)
- Treatment protocols (minocycline)
Fetal Alcohol Spectrum Disorder

- Alcohol-related birth defects (ARBD)
- Wide spectrum; evolves over time
- Most common preventable cause of birth defects
- 2-3/1000 births
- Classic FAS (microcephaly, ptosis, short palpebral fissures, washed-out philtrum)
FASD-Advances

- Spectrum encompasses infants with exposure, minimal variations (IOM)
- Epidemic in some international areas
- MD ARBD legislation
Neurofibromatosis

- 1/3000 births; 50% new; 70% mild
- Member of RAS/MAPK family
- NIH consensus criteria misleading <3 yrs
  - 6 or more CALS >0.5 cm
  - Axillary, inguinal freckling
  - Bony dysplasia
  - Positive family history
- Neurodevelopmental differences common
Neurofibromatosis-Advances

• 1/3 of patients with “Noonan” phenotype
• SPRED1/Legius syndrome (spots only)
• Controversies?
  – Baseline MRI (23% with optic pathway lesions)
  – Treatment options
RAS/MAPK Syndromes

• Includes Noonan syndrome, CFC syndrome, Costello syndrome (11 genes in pathway)
• Incidence 1/5000 births
• Variable/overlapping phenotype
• Diagnostic keys
  – Macrocephaly/LGA
  – Pale irises, ptosis
  – Redundant nuchal skin
  – Congenital heart disease (pulmonary stenosis, cardiomyopathy)
Noonan Syndrome-Management/Advances

• MAPK chip array
• ECHO
• CBC
• Renal sono
• Increased awareness bone marrow dysfunction, pediatric tumors (HRAS)
• Growth hormone supplementation
Marfan Syndrome

• Pediatric disorder; easily overlooked
• Incidence 1/15,000 births; 50% new
• Life-changing diagnosis
• Myopia, dolichostenomelia, arachnodactyly, mitral valve prolapse
• Differential: mitral valve prolapse-Marfanoid habitus syndrome, homocystinuria
Marfan Syndrome-Advances

• Cardiology consultation
• Molecular testing for fibrillin 1
• Loeys-Dietz syndrome (TGFBR1 and 2)
• Losartan for mutation positive patients
• Exercise restrictions
Achondroplasia

• Incidence 1/10,000 births
• Autosomal dominant (most new)
• Secondary to alteration in FGFR3
• Diagnostic keys
  – Short stature, macrocephaly, rhizomelic shortening
  – Trident hand
  – Characteristic radiologic findings
Achondroplasia-Management

• Exclude lethal disorder (thanatophoric dysplasia)
• Skeletal survey, molecular testing
• Evaluate chest
• MRI for foramen magnum size
Achondroplasia-Advances

• Potential need for surgery
  – Foramen magnum, hydrocephalus
  – Orthopedic
• Role for limb lengthening procedures
• National support groups
Osteogenesis Imperfecta

- Classic types (I-IV)
- Often diagnosed prenatally
- New types (V-XI)
- Use of bisphosphonate therapy
Prader-Willi Syndrome

- Incidence 1/15,000 births
- Most common syndromic cause of unexplained hypotonia
- Deletion of paternal 15q11.2 (70-80%)
- 20-30% maternal uniparental disomy (UPD)
- Childhood onset obesity
Prader-Willi Syndrome

• Diagnostic keys
  – Hypotonia
  – Bitemporal constriction
  – Tapered fingers
  – Undescended testes
  – Feeding inability
Prader-Willi Syndrome-Management

• Neurologic evaluation for hypotonia
  – CPK, electrodiagnostics?
• Feeding evaluation
• Rapid FISH or methylation studies
• Potential for sudden death
Prader-Willi Syndrome-Advances

- Aggressive GI/nutrition management
- Growth hormone supplementation
- Potential for pharmacologic intervention
- Increased risk for childhood/adolescent psychiatric disorders
Deletion 22q11.2

- Incidence 1/5000 births
- DiGeorge sequence/velocardiofacial syndrome
- Accounts for 1/3 of isolated conotruncal malformations
- 5-7% inherited
- Highly variable
Deletion 22q11.2

- Diagnostic keys
  - Prominent square nasal bridge
  - Small alae nasi
  - Long, tapered fingers
  - Cleft palate
  - Congenital heart disease (Tetralogy of Fallot, truncus arteriosus, VSD)
Deletion 22q11.2-Management

- FISH or microarray
- Evaluation for additional malformations
  - Cardiac, renal
- Immunologic workup, calcium metabolism
- Defer immunizations?
- Specialty consultation (Plastics)
Deletion 22q11.2-Advances

• Increased awareness of clinical spectrum/Low threshold for diagnosis
• Psychiatric disorders common, often difficult to manage
• National support groups
The Rest of the Best

- CHARGE syndrome
- Beckwith-Wiedemann syndrome
- Williams syndrome
- Kabuki syndrome
- de Lange syndrome
Resources

- www.genereviews.org
- www.clinicaltrials.gov
- www.geneticalliance.org
- Unique rare chromosome disorders support group
- NORD
- AAP Clinical Report for Practitioners: Health Supervision Guidelines for Individuals with Down Syndrome, 2011