Dysmorphology Differential and Testing

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The speaker has signed a disclosure form and indicated she has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

During this session the speaker will discuss the available genetic tests and the recommended approach depending on the patient’s presentation.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- list the characteristics of malformation sequences, associations, deformations, disruptions and dysplasias;
- describe the difference between major anomalies, minor anomalies and normal variants;
- list at least one indication each for ordering a chromosome, FISH and microarray analysis;
- list the major indications and components of biochemical genetic testing;
- describe the tiered approach to a work-up for hypotonia.

Resources

www.genetests.org Excellent reviews for physicians and other healthcare professionals
www.emory.genetics.edu/ Emory University Department of Human Genetics
www.kumc.edu/gec/support/ Genetic Conditions and Rare Conditions

Session Outline

See presentation handout on the following pages.
Dysmorphology Definition

- Denotes human congenital defects and abnormalities of body structure that originate before birth
- Knowing the terminology for how to evaluate and group dysmorphic features will help to determine what testing and other evaluations to consider

Malformation (poor formation)

- Malformation
  - PRIMARY DEFECT
  - Basic alteration of structure
  - Usually occurs in first 10 weeks of gestation
  - Examples:
    - Polydactyly
    - Omphalocele
    - Spina Bifida
    - Cleft lip or palate
    - Congenital Heart Defects

Malformation Syndrome

- A recurring pattern of structural defects or secondary effects/defects that arise from several different errors in morphogenesis
- The combination of features generally represents a specific etiology
- “Syndrome” (Greek) – running together
- Examples:
  - Single gene disorders – e.g. Smith-Lemli-Opitz syndrome
  - Chromosomal disorders – e.g. Down syndrome
  - Microdeletion syndrome – e.g. Williams syndrome
  - Multifactorial disorders – e.g. cleft palate
  - Environmental – e.g. Rubella, Infant of Diabetic Mother

Smith-Lemli-Opitz syndrome

Defect in Cholesterol Metabolism

- Ptosis
- Micrognathia
- Epicanthal folds
- Low set ears
- Prominent philtrum
- Cleft palate
- Toes 2-4 syndactyly
- Hypospadius in males
**Malformation Sequence**
- A pattern of multiple defects resulting from a single primary malformation
- Example: Pierre Robin sequence
  - micrognathia
  - low set ears,
  - glossoptosis causes U-shaped palate

**Malformation Association**
- A non-random occurrence of multiple anomalies which cannot be explained by chance alone - etiology unknown
  - Diagnosis of exclusion
- Generally there are six to eight core features,
  - Rarely are all present in the same child
- At least three to four features must be present to feel secure in the diagnosis of any association
- Example: VATER or VACTERL
  - Vertebral anomalies
  - Anal atresia
  - Cardiac anomalies
  - TOF fistula with EA
  - Renal anomalies
  - Radial dysplasia
  - Single umbilical artery

**Deformation (mechanical)**
- Deformation
  - SECONDARY DEFECT
  - The basic structure is normal, but problem occurs in the structure's position or maturation
  - Uterine malformation – bicornuate uterus, twins, oligohydramnios, breech position
  - Generally occurs after 10 weeks gestation
  - Examples:
    - Club feet – talipes deformity
    - Bowed limbs
    - Torticollis
    - Cranial contour aberrations

**Disruption (destructive)**
- Disruption
  - SECONDARY DEFECT
  - Destruction of tissue that was previously normal
  - Severe positional problem which alters normally formed structure into the appearance of an anomaly
  - Can occur any time during gestation
  - Examples:
    - Limb amputation secondary to amniotic bands
    - Local tissue ischemia
    - Hemorrhage

**Dysplasia (deregulation)**
- Abnormal cellular organization within tissue resulting in structural changes:
  - Neural crest cell migration abnormalities
    - Neurocutaneous melanosis
      - Giant pigmented nev, seizures and other CNS abnormalities
  - Skeletal dysplasias – involve cartilage or bone
    - Epiphyseal dysplasia
    - Spondyloepiphyseal dysplasia (spine involved)
    - Most skeletal dysplasias are associated with disproportionate short stature

**Impact of Malformations**
- Background risk is 3% for a significant congenital malformation at birth
- Malformations are responsible for a large proportion of neonatal and infant deaths
- Account for around 30% of admissions to pediatric hospitals
- Important to recognize both major and minor malformations as this may result in early detection and intervention
Major Anomaly
(may be isolated or multiple affecting different body systems)

- A basic alteration in embryological development which is
  - severe enough to require intervention, and
  - has the potential for long term impact medically and/or psychologically
  - Usually recognizable in the newborn period
  - Examples:
    - Spina bifida
    - Anophthalmia
    - Cleft lip/palate
    - Radial agenesis
    - Congenital Heart Defects

Minor Anomalies

- A basic alteration in embryological development which
  - either requires no treatment or
  - can be, more or less, totally corrected
  - can be detected any time throughout life
  - Examples:
    - Low set ears
    - Hypospadias
    - Postaxial polydactyly
    - Micrognathia (if severe, major anomaly)
    - VSD, ASD (if severe, major anomaly)

Normal or Minor Variant

- These features which have a low frequency (1%-5%) in the general population
  - However, may also be seen in MCA syndromes
  - Do not necessarily differ from minor anomalies
  - May be familial or of ethnic background
- Examples
  - Single transverse palmar crease (2-4% of gen population)
  - Nevus flammeus
  - Accessory nipple
  - “Absent” ear lobe
  - Epicanthal folds

When to Consider a “Dysmorphic Syndrome”

- One major or two minor anomalies
- Growth aberration (pre or post-natal)
- Cranial size or contour anomalies
  - Macrocephaly, microcephaly, etc.
- Neurologic problems
  - Seizures, hyper or hypotonia, intellectual disabilities
- Ectodermal defects
  - Teeth, nails, pigment, hair, skin

When to Consider a “Dysmorphic syndrome”

- Orthopedic problems
  - Joint hypermobility or dislocation, contractures, scoliosis, kyphosis, multiple fractures
- Abnormal sexual development
- Unusual behavior, activity or speech
- Phenotypic variation from parents or sibs
- Miscellaneous:
  - Deafness, blindness or other degree of visual loss

Dysmorphology Approach
Family and Prenatal History

- Family history (three generations)
- Photographs of close relatives at various ages
- Prenatal History:
  - Maternal exposures
    - drugs/medications/chemical/x-ray
  - Maternal illnesses
  - Fetal position and activity
  - Uterine constraints
  - Amniotic fluid volume
    - Oligohydramnios and polyhydramnios
<table>
<thead>
<tr>
<th>Dysmorphology Approach</th>
<th>Dysmorphology Approach</th>
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<tbody>
<tr>
<td><strong>Delivery History</strong></td>
<td><strong>Neonatal History</strong></td>
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<tr>
<td>• Delivery History</td>
<td>• Apgar scores and respiratory status</td>
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<tr>
<td>– Vaginal vs C-section</td>
<td>• Birth parameters and plot on appropriate graph</td>
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<tr>
<td>– Forceps or vacuum assisted vs spontaneous</td>
<td>– Weight</td>
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<td>– Induced vs non-induced</td>
<td>– Length</td>
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<tr>
<td>• Other difficulties</td>
<td>– Head circumference</td>
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<td>– Fetus or mother</td>
<td>– Chest circumference</td>
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<tr>
<td><strong>Patient’s Past Medical History</strong></td>
<td><strong>Specific Medical Problems</strong></td>
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<tr>
<td>• Growth</td>
<td>• Feeding</td>
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<td>• Development</td>
<td>• Neurologic</td>
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<tr>
<td>• General Health</td>
<td>• Cardiac</td>
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<td>• New or persisting problems</td>
<td>• Physical Anomalies</td>
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<tr>
<td>• Previous surgeries</td>
<td><strong>Try to Obtain Medical Records</strong></td>
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<td>• Previous hospitalizations</td>
<td>• This can be tedious and time consuming</td>
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<td><strong>Dysmorphology Approach</strong></td>
<td>• Never assume the verbal history by the family is correct</td>
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<td><strong>Detailed Physical Exam</strong></td>
<td>• One of the most common causes for a wrong diagnosis is not having all the previous medical tests and information</td>
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<td>• Detailed Physical Exam</td>
<td><strong>Develop a Differential Diagnosis</strong></td>
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<td>– Ht, Wt and HC – plot on appropriate growth curves</td>
<td>• Lock onto the rarest anomaly for quicker diagnosis</td>
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<tr>
<td>– Other anthropometric measurements as indicated</td>
<td>• Develop Differential Diagnosis:</td>
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<td>– Short stature (height below -3 SD)</td>
<td>– Determine major vs minor anomaly</td>
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<tr>
<td>– Tall stature (height above +3 SD)</td>
<td>– Determine minor anomaly vs normal variant</td>
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<td>– Failure to Thrive (Ht and Wt below -3SD)</td>
<td>• Compare:</td>
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<tr>
<td>• Symmetrical vs non-symmetrical growth – is there head sparing?</td>
<td>– Bilateral and adjacent structures</td>
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<td>– Obesity (weight above +3SD)</td>
<td>– Compare to other family members in person or photos</td>
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<td>– Compare to “typical” individuals in that ethnicity</td>
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<td>• When did the problem most likely occur?</td>
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<td>– Prenatal (prior to 10 weeks – true malformation)</td>
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<td>– Perinatal (CNS damage from hypoxia)</td>
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<td>– Postnatal (normal appearing at birth then develops dysmorphic features – metabolic or storage dx)</td>
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Work up for Dysmorphology

• Standard chromosome analysis (approximately 450-550 bands: yield ~5 percent)
  – Use this only if suspect
    • major trisomy 13, 18, or 21
    • Turner and Klinefelter syndrome etc.
    • Ambiguous genitalia
    • Parental chromosomes with history of more than 2 miscarriages
  
• FISH if strongly suspect a specific microdeletion syndrome: (yield depends on features identified)
  – E.g. 22q11.2, Williams, Smith Magenis

• Chromosomal microarray if dysmorphic features but not striking for major trisomy (yield ~20 percent)
  – Arrays include all the known microdeletion and microduplication syndromes

Consider Brain Imaging

• Cranial size or contour aberrations
• Hypertelorism, hypotelorism, colobomas
• Facial clefts
• Cleft lip and/or palate (especially midline clefts)
• Single upper central incisor
• Neurological Symptoms
  – Seizures
  – Problems with tone
  – Intellectual Disability

Consider X-rays

• Chest X-ray:
  – count the ribs and look at structure (bifid)
  – segmentation anomalies of the vertebrae
• Skeletal survey for:
  – Proportionate or disproportionate aberrations
  – Recurrent fractures
• Specific X-rays for:
  – Discrepancy in size (ie Short forearms, absent thumbs)
  – Contour abnormality (Bowed bones, scoliosis)
  – Asymmetry
  – Dislocations

Consider Echocardiogram

• Abnormal auscultation findings
• Known syndromes with cardiac findings diagnosed by FISH or chromosomal microarray
  – Williams syndrome
    • Supravalvular aortic stenosis
    • Peripheral Pulmonary Artery Stenosis
  – 22q11.2 deletion (aka DiGeorge syndrome)
    • Conotruncal cardiac anomalies: IAA, TA, TOF
Consider Ultrasounds

- Abdominal - organomegaly
- Renal – dysplastic or horseshoe kidney
- Pelvic – reproductive organs in ambiguous genitalia

**Metabolic Disorders with Dysmorphisms:**
- Coarse features, large fontanels, high forehead, ptosis, flat facies, cataracts, hypoplastic optic discs
- **Lysosomal Storage Disorders** (e.g. Hurler syndrome)
  - Screen with oligosaccharides and mucopolysaccharides
  - If positive or continued suspicion → lysosomal enzyme panel
- **Peroxisomal Disorders** (e.g. Zellweger syndrome)
  - Very Long Chain Fatty Acids, Phytanic and Pristanic acids
- **Cholesterol synthesis disorders** (e.g. Smith-Lemli-Opitz)
  - Serum cholesterol (low) and
  - 7 de-hydrocholesterol (high)

**Dysmorphology Differential**

- General rules of thumb:
  - Involvement of bilateral structures over unilateral structures are more likely to have a genetic etiology
  - Deformation sequences usually have a better prognosis than malformation sequences
  - Deformation sequences usually have a very low recurrence risk
  - Specific diagnoses usually depend on the total pattern of anomalies
    - Even rare defects can be found in multiple syndromes with various etiologies

- **Suspected Metabolic Disorder without overtly Dysmorphic Features**
  - Unexplained coma
  - Seizures
  - Vomiting, diarrhea or unusual odor
  - Visceromegaly
  - Cataracts
  - Thick, lax or hyperelastic skin
  - Regression of psychomotor skills

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Jones, KL et al. Smith’s Recognizable Patterns of Human Malformation: Elsevier Saunders, Sixth Ed., p. 3.
Genetic Biochemical Studies

- Basic work up in neonates
  - Plasma amino acids
  - Plasma carnitine (total and free)
  - Plasma acylcarnitine profile
  - Urine organic acids
- If organomegaly or loss of milestones
  - Urine oligosaccharides
  - Urine mucopolysaccharides
- If coma or seizures
  - Ammonia
  - Glucose
  - Electrolytes
  - Blood lactate and pyruvate

Molecular Studies

- Generally done when a specific disorder is suspected
  - Gene Sequencing for specific gene
    - SMN1 gene for Spinal Muscular Atrophy
    - Hypotonia, absent DTRs, tongue fasciculations
  - Gene sequencing panels
    - Hypotonia panel: SMA, Myotonic Dystrophy, Prader Willi, Angelman syndrome, maternal UPD 14
    - Whole exome sequencing
      - Usually want geneticist involved to order this test

Hypotonia work up

- First tier (no encephalopathy):
  - Chromosomal microarray
  - Hypotonia panel at Emory Genetics Lab includes:
    - Spinal Muscular Atrophy
    - Myotonic Dystrophy
    - Prader-Willi /Angelman
    - Maternal UPD 14
  - Carnitine – total and free
  - CPK
  - Neurology consult
    - Brain imaging recommendations
    - Muscle and nerve biopsy recommendations

Hypotonia work up

- Second tier (encephalopathy signs – seizures, non-responsive, not tracking):
  - Basic Metabolic Studies:
    - Plasma amino acids, carnitine, acylcarnitine profile (FAO defects), urine organic acids
    - Ammonia (Urea cycle defects)
    - Lactate and pyruvate (Mitochondrial disorders)
    - Very long chain fatty acids (Peroxisomal disorders)
  - Urine for Oligosaccharides and Mucopolysaccharides (Lysosomal disorders)
  - Neurology consult for recommendations:
    - Muscle and nerve biopsy and brain imaging

Hypotonia work up

- Third tier:
  - Congenital muscular dystrophy panel (numerous)
    - Choice of panel depends on clinical exam
    - Neuromuscular imaging (MRI)
    - Electromyography
    - Muscle biopsy
  - Pompe disease

- Fourth tier:
  - Mitochondrial array

Case Example: 9 day old male, hypotonia, swallowing dysfunction, poor movements

- Microarray – normal
- CPK – normal
- Metabolic panel: AA, OA, carnitine, acylcarnitine profile – all normal
- Very Long Chain Fatty Acids - normal

So the answer came from the Brain MRI:
1. The pons is small in size with flattening of the anterior margin
2. Dysmorphic basal ganglia
When to Refer to Genetics

Rule of Thumb

1 major or 2 minor birth defects
Development delay of unknown cause
2 or more dysmorphic features