Case Based Syndrome Evaluation by US / MR

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General Principles of Fetal Imaging

- Most fetuses look normal
- Normal = the same as other same age fetuses
- If a fetus looks different, it may be abnormal
- Some anomalies are serious; Others are not
- Multiple anomalies raise risk of syndromes and chromosomal anomalies

Structural Defects

- Major 3-4%
- Minor 7-10%
- Isolated vs. multiple
- Pattern recognition is critical

Malformation Risk

- Disproportionately affect fetuses & newborns

Single Gene (Mendelian) Diseases Disproportionately Affect Fetuses & Newborns

- ~3500 genetic diseases with molecular basis
- ~50% of NICU admissions have genetic problem
- Clinical manifestation of Genetic diseases

How to detect a chromosome anomaly?

- Ex: Trisomy 21
- Until recently: ultrasound markers and findings:
  - EIF, echogenic bowel, nuchal fold, pyelectasis,
    absent nasal bone, major anomaly (CAVC, duodenal atresia)
  - Detected approximately 2/3 of cases of T21
- Past ~5 years:
  - Cell-free fetal DNA in maternal blood
  - Greater than 95% accuracy screening for
    T13, 18, 21, X0 + gender. New: microdeletions
Important terms
(We won’t cover)

• Karyotype
• Single point mutations
• Mutation panels
• Microarrays for microdeletions/insertions
• Single gene exon sequencing
• Whole exome sequencing
• Whole genome sequencing

Teratology

• The branch of medical science concerned with the development of physical abnormalities during the fetal or early embryonic stage

• The biological study of birth defects

• Relies on pattern recognition

Useful Terms in Teratology
(We will cover)

• Aneuploidy
• Malformation
• Deformation
• Dysplasia
• Syndrome
• Association
• Sequence
• Spectrum

Pattern recognition

• In fetal life, imagers are the eyes of the geneticist and clinician

• Need to know what fetal anomalies are present in order to make a diagnosis
ON-LINE RESOURCES

<table>
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<tr>
<th>Resource</th>
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<tr>
<td>Online Mendelian Inheritance in Man (OMIM)</td>
<td><a href="http://www.OMIM.org">http://www.OMIM.org</a></td>
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<tr>
<td>Skeletal Dysplasia Information and Diagnosis</td>
<td><a href="http://www.skeldys.org">http://www.skeldys.org</a></td>
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<tr>
<td>Gene Reviews</td>
<td><a href="http://www.ncbi.nlm.nih.gov/books/NBK1116/">http://www.ncbi.nlm.nih.gov/books/NBK1116/</a></td>
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<td>International Skeletal Dysplasia Society (ISDS)</td>
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<td>Connective Tissues Gene Tests (CTGT)</td>
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<tr>
<td>ARUP Consult</td>
<td><a href="http://www.arupconsult.com/">http://www.arupconsult.com/</a></td>
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<tr>
<td>European Skeletal Dysplasia Network (ESDN)</td>
<td><a href="http://www.esdn.org/eug/Home">http://www.esdn.org/eug/Home</a></td>
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Useful Terms in Teratology

(We will cover)

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- Malformation
- Deformation
- Dysplasia
- Syndrome
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- Sequence
- Spectrum

Aneuploidy

- Having a chromosome complement that is not an exact multiple of the haploid number, with either fewer or more than the normal number of chromosomes in the cell

Examples of aneuploidy

- Trisomy 21
- Triploidy (69XXX or 69XXY)

Nuchal translucency- 10 wks

Profile- 20 weeks
Combined Duodenal and Esophageal Atresia

Referral History

- 30 year old woman
- Referred for poor fetal growth
- Short long bones
- Abnormal placenta
Triploidy

- Presence of a complete extra set of chromosomes = total of 69 XXX or XXY
- Very common
- 1% of all conceptions
- 25% all 1st trimesters miscarriages
- 1/2500 births

Triploidy: Clinical Features

- Severe growth delay
- Head much larger than body
- Multiple anomalies: cleft lip/palate, micrognathia, holoprosencephaly, ACC, syndactyly, cardiac defects, omphalocele, renal anomalies
- Placental abnormalities

Malformation

- Morphologic defect of organ or body part
- Intrinsically abnormal early development
- Example: open neural tube defect
  - Failure of the neural tube to close
Referral History

- 32 year old G1 P0 woman
- Hydrocephalus: ?spina bifida
- Gestational age: 18 weeks, 3 days
- Declined AFP and amniocentesis
Deformation

- Abnormal form, shape or position of body part
- Due to mechanical forces
- Example: Club foot
Dysplasia

- Morphologic result of abnormal organization of cells into tissue

- Examples
  - cystic renal dysplasia secondary to obstruction
  - skeletal dysplasia

History

- Referral to Pediatric Urology for abnormal fetal kidneys at 25 weeks gestation

- Mild left fetal hydronephrosis

- Cysts in right fetal kidney

- 41 year old G4 P2 woman
- Naturally conceived pregnancy
- 19 week US? lethal dwarfism
- ? Thanatophoric dysplasia
19w3d but long bones ~14 week size

Platyspondyly

Short ribs
Summary of imaging findings @ 19w3d

- Micromelia all long bones
- Lagging behind GA by >5 weeks
- Femora bowed, angulated, normally mineralized
- Short ribs
- Small fetal chest, prominent abdomen
- Low-set ears
- Mild midface hypoplasia
- Frontal bossing
- Spine: ? platyspondyly

Possible Dx

- Lethal skeletal dysplasia
- Thanatophoric dysplasia vs other

Outcome

TAB
Autopsy

Small chest
Short limbs

Flattened (H-shaped) vertebrae
- Short ribs with a narrow chest
- Bowing of femur and humeri with wide metaphyses
- Small pelvis and scapulae

64 grams. Unusual secondary folds/gyri in temporal and parietal lobes
Thanatophoric dysplasia

- Incidence: 1 per 10,000 births.
- Thanatophoric' = death-bearing' - pulmonary hypoplasia leads to early death
- Type I - curved long bones, platyspondyly
- Type II, long bones relatively straight, platyspondyly less severe, cloverleaf skull

Association

- Nonrandom occurrence of multiple anomalies
- Seen in two or more individuals
- Example: VACTERL, CHARGE

VACTERL Association

- Acronym coined in 1972
- Vertebral defects
- Anal atresia
- Cardiac anomalies
- Tracheoesophageal fistula
- Renal anomalies
- Limb anomalies

Sequence

- Pattern of multiple anomalies, a cascade
- Derived from single known or presumed prior anomaly or mechanical factor
- Example: Robin sequence
Referral history

- 38 year old G1 P0 woman
- Failed IVF procedures
- Spontaneous pregnancy
- Fetus with severe micrognathia seen at 15.5w

Robin Sequence

- Cleft palate
- Micrognathia
- Glossoptosis
Robin Sequence

• Primary abnormality: ? small mouth
• Tongue falls back= glossoptosis
• Inhibits fusion of palate leading to cleft

Robin Sequence: Prenatal Diagnosis

• Polyhydramnios
• Micrognathia
• High arched cleft palate

Robin Sequence: Prognosis and Management

• Concern for upper airway obstruction
• Neonatal respiratory distress
• Feeding problems
• If survive infancy, jaw variably grows, and child often does well
• Autosomal recessive recurrence risk
• Differential dx micrognathia: T13, T18

Syndrome

• Pathogenically related pattern of multiple anomalies
• Single gene defect
• Chromosome abnormality or microdeletion
• Inborn error of metabolism

Referral History

• 40 year old woman referred by Genetics for fetal foot and hand anomalies
• 20 weeks gestation
Apert Syndrome

- Aka: Acrocephalosyndactyly
- Rare developmental deformity
- Craniofacial and limb malformations
- Variable degrees of developmental delay

Apert Syndrome: Genetics

- Falls within the fibroblast growth factor receptor related craniosynostosis syndromes (FGFR)
- Apert, Pfeiffer, Crouzon, Muenke, many others
- Family of 5 tyrosine kinase receptors
- Bind to group of 17 fibroblast growth factors
- FGF’s help regulate cell proliferation, differentiation and migration
- Important in angiogenesis, wound healing, malignant transformation, spermatogenesis
Prenatal Dx of Craniosynostosis

- Difficult to identify before 20 weeks
- Abnormal skull shape
- Midface hypoplasia
- Frontal bossing
- Hypertelorism and proptosis
- Anomalies of hands and feet: brachydactyly, syndactyly

History

- 34 year old G1 P0 woman
- 31 weeks 3 days gestation
- Referring diagnosis: Enlarged, echogenic kidneys, absent vermis, megacisterna magna

Prior imaging

- Normal US @ 12, 18, 23 weeks

Fluid in stomach, bladder, normal AFI
Summary of imaging findings
31 weeks 3 days

- Absent vermis
- Molar tooth configuration of brainstem: Joubert syndrome
- Enlarged, echogenic kidneys
- Normal amniotic fluid

Joubert Syndrome
- Rare brain malformation
- Absence of vermis, malformed brainstem
  - Molar tooth sign
- Infant symptoms: hyperpnea, hypotonia, abnormal eye movement, developmental delay, ataxia, seizures
- Polydactyly, CLP, kidney and liver abnormalities
- Sporadic or AR via >10 genes (ie: NPHP1)

Spectrum
- Any of a group of disorders each having symptoms that occur on a continuum
- Certain features are shared along its spectrum but that manifest in markedly different forms and degrees.

Spectrum
- Example: Dandy-Walker spectrum
In Summary

• Most fetuses look “normal”= the same
• If a fetus looks different, worry
• An isolated anomaly usually has better prognosis
• Multiple anomalies increase risk of chromosomal abnormality or a syndrome
• Become or befriend a geneticist!

Thank you!